

FOR OFFICIAL USE ONLY

U.S. DEPARTMENT OF COMMERCE  
Patent and Trademark Office

## 23350 SEARCH REQUEST FORM

Examiner # (Mandatory): K. Weddington Requester's Full Name: \_\_\_\_\_Art Unit 11614 Location (Bldg/Room#): CPA-2A17 Phone (circle 305 306 (308) 4650)Serial Number: 08/804,903 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention \_\_\_\_\_

Inventors (please provide full names): Robert B. PieveleyEarliest Priority Date: 2-24-97

Keywords (include any known synonyms registry numbers, explanation of initialisms):

The insulin sensitizer is selected from BRL-49653,  
~~Big~~ Pioglitazone, troglitazone, MC 555, ALRT 208,  
LGD 1064, chronic Picolinate and V-411.

The anti-diabetic agent is insulin

## Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

A method for the treatment of diabetes mellitus  
with a composition comprising

- 1) an insulin sensitizer
- 2) an anti-diabetic agent

RECEIVED  
SEC 22 1999  
JAN 13 1999

## STAFF USE ONLY

Searcher: <u>Stephenson</u>	Type of Search	Vendors (include cost where applicable)
Searcher Phone #: <u>308-4499</u>	<input type="checkbox"/> N.A. Sequence	<input type="checkbox"/> STN
Searcher Location: _____	<input type="checkbox"/> A.A. Sequence	<input type="checkbox"/> Questel/Orbit
Date Picked Up: _____	<input type="checkbox"/> Structure (#)	<input type="checkbox"/> Lexis/Nexis
Date Completed: <u>12/27/99</u>	<input type="checkbox"/> Bibliographic	<input type="checkbox"/> WWW/Internet
Clerical Prep Time: _____	<input type="checkbox"/> Litigation1	<input type="checkbox"/> In-house sequence systems (list)
Terminal Time: _____	<input type="checkbox"/> Fulltext	<input type="checkbox"/> Dialog
Number of Databases: _____	<input type="checkbox"/> Procurement	<input type="checkbox"/> Dr. Link
	<input type="checkbox"/> Other	<input type="checkbox"/> Westlaw
		<input type="checkbox"/> Other (specify)

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 17:12:27 ON 27 DEC 1999  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 1999 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications.

FILE COVERS 1967 - 27 Dec 1999 VOL 132 ISS 1  
FILE LAST UPDATED: 26 Dec 1999 (19991226/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=>

=>

=> d stat que l11

L1 14 SEA FILE=REGISTRY ABB=ON PLU=ON BRL 49653?/CN OR PIOGLITAZONE  
?/CN OR TROGLITAZONE?/CN OR (MC(W)555 OR MC555 OR ALRT268 OR  
ALRT(W)268 OR LGD(W)1069 OR PICOLINATE?(5A)CHROM? OR V411 OR  
4(W)411)  
L2 5272 SEA FILE=REGISTRY ABB=ON PLU=ON INSULIN/BI  
L3 903 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR BRL(W)49653? OR  
PIOGLITAZONE? OR TROGLITAZONE? OR MC(W)555 OR MC555 OR ALRT268  
OR ALRT(W)268 OR LGD(W)1069 OR PICOLINATE?(5A)CHROM? OR V411  
OR V(W)411  
L4 113076 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 OR ?INSULIN?  
L7 287 SEA FILE=HCAPLUS ABB=ON PLU=ON L3(5A)L4  
L8 125 SEA FILE=HCAPLUS ABB=ON PLU=ON L3(L)SENSITIZ?  
L9 98 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND L7  
L10 76 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 AND ?DIABET?  
L11 60 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND (TREAT? OR THERAP? OR  
MEDICIN? OR PHARAC? OR DRUG#)

=>

=>

=> d ibib abs hitrn l11 1-60

L11 ANSWER 1 OF 60 HCAPLUS COPYRIGHT 1999 ACS  
ACCESSION NUMBER: 1999:777981 HCAPLUS  
TITLE: A comparison of **troglitazone** and metformin  
on **insulin** requirements in euglycemic  
intensively insulin-treated type 2  
**diabetic** patients  
AUTHOR(S): Yu, Joseph G.; Kruszynska, Yolanta T.; Mulford, Mim  
I.; Olefsky, Jerrold M.  
CORPORATE SOURCE: Department of Endocrinology and Metabolism, University  
of California San Diego, La Jolla, CA, 92093, USA  
SOURCE: Diabetes (1999), 48(12), 2414-2421

CODEN: DIAEAZ; ISSN: 0012-1797  
PUBLISHER: American Diabetes Association  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB **Troglitazone** and metformin lower glucose levels in **diabetic** patients without increasing plasma insulin levels. We compared the insulin sparing actions of these two agents and their effects on insulin sensitivity and insulin secretion in 20 type 2 **diabetic** patients. To avoid the confounding effect of improved glycemic control on insulin action and secretion, patients were first rendered euglycemic with 4 wk of continuous s.c. insulin infusion (CSII) before randomization to CSII plus **troglitazone** (n = 10) or CSII plus metformin (n = 10); euglycemia was maintained for another 6-7 wk. Insulin sensitivity was assessed by a hyperinsulinemic-euglycemic clamp (1) at baseline, (2) after 4 wk of CSII, and (3) after CSII plus either **troglitazone** or metformin. The 24-h glucose, insulin, and C-peptide profiles were performed on the day before the second and third glucose clamps. Good glycemic control was achieved with CSII alone and was maintained with CSII plus an oral agent (mean 24-h glucose: **troglitazone**, 6.2  $\pm$  0.6 mmol/l; metformin, 6.2  $\pm$  0.3 mmol/l). **Insulin** requirements decreased 53% with **troglitazone** compared with CSII alone (48  $\pm$  0.4 vs. 102  $\pm$  0.13 U/day, P < 0.001), but only 31% with metformin (76  $\pm$  0.13 vs. 110  $\pm$  0.18 U/day, P < 0.005). The 24-h C-peptide profiles were similar. Normal fasting hepatic glucose output was maintained with both agents despite lower insulin levels than on CSII alone. Insulin sensitivity did not change significantly with CSII alone or with CSII plus metformin, but improved 29% with CSII plus **troglitazone** (P < 0.005 vs. CSII alone) and was then 45% higher than in the CSII plus metformin patients (P < 0.005). In conclusion, metformin has no effect on insulin-stimulated glucose disposal independent of glycemic control in type 2 **diabetes**. **Troglitazone** (600 mg/day) has greater **insulin**-sparing effects than metformin (1,700 mg/day) in CSII-treated euglycemic patients. This is probably explained by the peripheral tissue **insulin-sensitizing** effects of **troglitazone**.

L11 ANSWER 2 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:684556 HCAPLUS

DOCUMENT NUMBER: 131:346342

TITLE: Troglitazone prevents mitochondrial alterations, .beta. cell destruction, and **diabetes** in obese **prediabetic** rats

AUTHOR(S): Higa, Moritake; Zhou, Yan-Ting; Ravazzola, Mariella; Baetens, Danielle; Orci, Lelio; Unger, Roger H.

CORPORATE SOURCE: Gifford Laboratories, Center for Diabetes Research, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, 75235, USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1999), 96(20), 11513-11518

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To det. whether the **antidiabetic** action of **troglitazone** (TGZ), heretofore attributed to **insulin sensitization**, also involves the protection of .beta. cells from lipoapoptosis, the authors **treated prediabetic Zucker Diabetic Fatty** rats with 200 mg/kg per day of TGZ. Their plasma-free fatty acids and triacylglycerol fell to 1.3 mM and 111 mg/dL, resp., compared with 2.0 mM and 560 mg/dL in untreated controls. Their islet triacylglycerol content was 34% below controls. In islets of control rats, .beta. cells were reduced by 82% and the islet architecture was disrupted; .beta.-cell glucose transporter 2 was absent, 85% of their mitochondria were altered, and they were unresponsive to glucose. In **treated** rats, the loss of .beta. cells was prevented, as were the loss of .beta. cell glucose transporter 2, the mitochondrial alterations, and the impairment

of glucose-stimulated insulin secretion. Thus, the **antidiabetic** effect of TGZ in **prediabetic** Zucker **Diabetic** Fatty rats involves prevention of lipotoxicity and lipoapoptosis of .beta. cells, as well as improvement in insulin sensitivity.

IT **9004-10-8, Insulin**, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(**troglitazone** prevents mitochondrial alterations and .beta. cell destruction and **diabetes** in obese **prediabetic** rats)

L11 ANSWER 3 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:642128 HCAPLUS

DOCUMENT NUMBER: 131:237406

TITLE: The polycystic ovary syndrome: **treatment** with insulin sensitizing agents

AUTHOR(S): Iuorno, Maria J.; Nestler, John E.

CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Internal Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, USA

SOURCE: Diabetes, Obes. Metab. (1999), 1(3), 127-136

CODEN: DOMEF6; ISSN: 1462-8902

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 69 refs. This article reviews ovarian insulin signalling in polycystic ovary syndrome (PCOS), hyperinsulinemia and hyperandrogenism in PCOS, and **treatment** with **insulin-sensitizing** agents metformin and **troglitazone**.

IT **97322-87-7, Troglitazone**

RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)

(**treatment** of polycystic ovary syndrome with insulin **sensitizing** agents)

L11 ANSWER 4 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:632690 HCAPLUS

DOCUMENT NUMBER: 131:331950

TITLE: Troglitazone increases cytochrome P-450 3A protein and activity in primary cultures of human hepatocytes

AUTHOR(S): Ramachandran, Vinod; Kostrubsky, Vsevolod E.; Komoroski, Bernard J.; Zhang, Shimin; Dorko, Kenneth; Esplen, James E.; Strom, Stephen C.; Venkataramanan, Raman

CORPORATE SOURCE: Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA, USA

SOURCE: Drug Metab. Dispos. (1999), 27(10), 1194-1199

CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Troglitazone** (TRO) is an **insulin sensitizer**

used in the **treatment** of type II **diabetes**. TRO is known to increase the activity of cytochrome P 450 (CYP) 3A in vivo. We have investigated the effect of TRO on CYP3A protein content and the activity of CYP3A (as measured by the formation of 6.beta.-hydroxytestosterone formation) in primary cultures of human hepatocytes in comparison with rifampicin (RIF). Hepatocytes were isolated from four human livers by perfusion with collagenase, plated on collagen-coated plates, and maintained in William's E medium. After 48 h in culture, cells were exposed to RIF (10 .mu.M) or TRO (0-50 .mu.M) twice, each over a period of 24 h, and the activity of CYP3A was measured. TRO increased the activity of CYP3A in a concn.-dependent manner, reaching a maximal response at 5 .mu.M. Pretreatment of the hepatocytes with 10 .mu.M TRO or 10 .mu.M RIF resulted in a 4- to 15-fold increase in the activity of

CYP3A. Max. increase in CYP3A protein was obsd. at 5 .mu.M TRO. There was a significant correlation ( $R^2 = 0.89$ ) between the content of immunoreactive CYP3A protein in the hepatocytes and the rate of formation of 6.beta.-hydroxytestosterone. These results indicate that TRO is a potent inducer of CYP3A and is similar to RIF in inducing CYP3A in human hepatocytes. At concns. of 25 .mu.M and above, TRO was toxic to the cells, as detd. by a decrease in the activity of CYP3A, a redn. in the amt. of immunoreactive protein, and changes in the morphol. of the cells.

L11 ANSWER 5 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:606001 HCAPLUS  
DOCUMENT NUMBER: 131:294992  
TITLE: Insulin sensitizers - a new global attack on insulin resistance and the metabolic syndrome  
AUTHOR(S): Goke, Burkhard  
CORPORATE SOURCE: Clinical Research Unit for Gastrointestinal Endocrinology, Department of, Philipps University of Marburg, Marburg, 35033, Germany  
SOURCE: Adv. Lipoprotein Atheroscler. Res., Diagn. Treat., Proc. Int. Dresden Lipid Symp., 9th (1998), Meeting Date 1997, 101-107. Editor(s): Hanefeld, Markolf. Fischer: Jena, Germany.  
CODEN: 68EPAR  
DOCUMENT TYPE: Conference; General Review  
LANGUAGE: English

AB A review with 22 refs. The pathophysiol. of **diabetes** mellitus type II is complex. It consists of peripheral insulin resistance, hepatic insulin resistance resulting into an increased hepatic glucose prodn., and impaired insulin secretion. Regardless of the etiol. sequence of events, it is evident that insulin resistance is the characteristic feature of the vast majority of patients with type II **diabetes** and contributes significantly to the occurrence of hyperglycemia. The logical and rational **therapeutic** approach is therefore to improve the insulin resistant state by an appropriate pharmacol. intervention. This has already been tried by the classically utilized **drugs** such as sulfonylureas, metformin, and glucosidase inhibitors. However, their resp. impact on insulin resistance is either relatively small or an only indirect effect mediated by reduced hyperglycemia with consecutively diminished glucose toxicity. The new class of thiazolidinedione compds. (glitazones), resembles a direct approach to improve insulin sensitivity in the target tissues. This brief overview aims to summarize and focus on recent discoveries explaining potential mechanisms of glitazone action and to summarize important clin. data which nourish the hope for a more successful approach to the **treatment** of insulin resistance.

IT 97322-87-7, **Troglitazone**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**insulin sensitizers**, a new global attack on insulin resistance and metabolic syndrome)

L11 ANSWER 6 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:602172 HCAPLUS  
DOCUMENT NUMBER: 131:295422  
TITLE: Improvement in insulin resistance and the restoration of reduced phosphodiesterase 3B gene expression by pioglitazone in adipose tissue of obese **diabetic** KKAY mice  
AUTHOR(S): Tang, Yan; Osawa, Haruhiko; Onuma, Hiroshi; Nishimiya, Tatsuya; Ochi, Masa-Aki; Makino, Hideichi  
CORPORATE SOURCE: Department of Laboratory Medicine, Ehime University School of Medicine, Ehime, 791-0295, Japan  
SOURCE: Diabetes (1999), 48(9), 1830-1835  
CODEN: DIAEAZ; ISSN: 0012-1797  
PUBLISHER: American Diabetes Association  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Phosphodiesterase (PDE) 3B is a key enzyme in the mediation of the

antilipolytic action of insulin in adipocytes, and activation of this mol. results in a reduced output of free fatty acids (FFAs). An elevation of serum FFAs is known to cause insulin resistance in skeletal muscle and liver, which could be the primary cause of type 2 **diabetes**. To elucidate whether PDE3B is involved in this disease, we examd. the PDE3B gene expression in epididymal fat tissues of obese insulin-resistant **diabetic** KKAY mice. We also examd. the effect of an

**insulin-sensitizing drug, pioglitazone**

, on this gene expression. In adipose tissue of KKAY mice, PDE3B mRNA and its corresponding protein were reduced to 48 and 43% of those in C57BL/6J control mice. Basal and insulin-stimulated membrane-bound PDE activities were also decreased to 50 and 36% of those in the controls, resp.

**Pioglitazone** increased both PDE3B mRNA and protein levels by 1.8-fold of those in untreated KKAY mice. Basal and insulin-induced membrane-bound PDE activities were also increased by 1.6- and 2.0-fold, resp. **Pioglitazone** reduced the elevated levels of serum insulin, glucose, FFAs, and triglyceride in KKAY mice. Thus, the reduced PDE3B gene expression in adipose tissues could be the primary event in the development of insulin resistance in KKAY mice, which was improved by **pioglitazone** possibly because of the restoration of the reduced PDE3B gene expression.

IT **111025-46-8, Pioglitazone**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(improvement in **insulin** resistance and phosphodiesterase 3B

gene expression restoration by pioglitazone in adipose tissue of obese **diabetic** KKAY mice)

L11 ANSWER 7 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:509242 HCAPLUS

DOCUMENT NUMBER: 131:295413

TITLE: Troglitazone inhibits expression of the phosphoenolpyruvate carboxykinase gene by an insulin-independent mechanism

AUTHOR(S): Davies, G. F.; Khandelwal, R. L.; Roesler, W. J.

CORPORATE SOURCE: Department of Biochemistry, University of Saskatchewan, Saskatoon, SK, Can.

SOURCE: Biochim. Biophys. Acta (1999), 1451(1), 122-131

CODEN: BBACAQ; ISSN: 0006-3002

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Troglitazone** is an oral **insulin-sensitizing**

**drug** used to **treat** patients with type 2 **diabetes**

. A major feature of this hyperglycemic state is the presence of increased rates of hepatic gluconeogenesis, which **troglitazone** is able to ameliorate. In this study, we examd. the mol. basis for this property of **troglitazone** by exploring the effects of this compd.

on the expression of the two genes encoding the major regulatory enzymes of gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in primary cultures of rat hepatocytes.

Insulin is able to inhibit expression of both of these genes, which was verified in our model system. **Troglitazone** significantly

reduced mRNA levels of PEPCK and G6Pase in rat hepatocytes isolated from normal and Zucker-**diabetic** rats, but to a lesser extent than

that obsd. with insulin. Interestingly, **troglitazone** was unable to reduce cAMP-induced levels of PEPCK mRNA, suggesting that the mol.

mechanism whereby **troglitazone** exerted its effects on gene

expression differed from that of insulin. This was further supported by the observation that **troglitazone** was able to reduce PEPCK mRNA

levels in the presence of the insulin signaling pathway inhibitors

wortmannin, rapamycin, and PD98059. These results indicate that

**troglitazone** can regulate the expression of specific genes in an

insulin-independent manner, and that genes encoding gluconeogenic enzymes are targets for the inhibitory effects of this **drug**.

IT **9004-10-8, Insulin**, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**troglitazone** inhibits phosphoenolpyruvate carboxykinase and  
glucose-6-phosphatase genes by insulin-independent mechanism)

L11 ANSWER 8 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:493082 HCAPLUS

DOCUMENT NUMBER: 131:139180

TITLE: Vasodilatory effects of troglitazone improve blood  
pressure at rest and during mental stress in type 2  
**diabetes** mellitus

AUTHOR(S): Sung, Bong Hee; Izzo, Joseph L., Jr.; Dandona, Paresh;  
Wilson, Michael F.

CORPORATE SOURCE: Department of Medicine, State University of New York,  
Buffalo, NY, USA

SOURCE: Hypertension (1999), 34(1), 83-88

CODEN: HPRTDN; ISSN: 0194-911X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The present study examd. the hemodynamic mechanisms of blood pressure (BP)  
lowering by **troglitazone** in patients with type 2

**diabetes** mellitus (DM) at rest and during a mental arithmetic test  
(MAT). Twenty-two patients with DM with normal to high-normal BP and 12  
controls matched for age, gender, glucose tolerance, and BP were studied.  
DM subjects showed significantly higher systolic BP response during MAT  
than controls (157 vs. 139 mm Hg;  $P < 0.01$ ). All 22 DM patients and 5 of 12  
controls had systolic BP  $> 140$  mm Hg during MAT. Heart rate and diastolic  
BP were not significantly different between the 2 groups. The DM group  
was then randomized to receive **troglitazone** ( $n=10$ ; 400 mg/d) or  
glyburide ( $n=12$ ; 20 mg/d). MAT was repeated after 6 mo of  
**treatment**. Both **treatments** reduced glucose equally  
( $-1.7$  mmol/L for **troglitazone** and  $-1.5$  mmol/L for glyburide),  
but only **troglitazone** reduced **insulin** ( $-15$  . $\mu$ .U/mL;  
 $P < 0.001$ ) and C-peptide ( $-0.9$  ng/mL;  $P < 0.02$ ) levels. **Troglitazone**  
significantly reduced BP at baseline ( $P < 0.05$ ) and systolic BP response to  
MAT ( $P < 0.01$ ), whereas glyburide did not affect BP at baseline or during  
MAT. Stroke vol. and cardiac output did not change with either  
**drug**, but **troglitazone** decreased peripheral vascular  
resistance ( $-112$  dyne .cntdot. s .cntdot. cm $^{-5}$ ;  $P < 0.05$ ). Improved insulin  
resistance rather than an improved glycemic control is assocd. with lower  
resting and stress BP values in patients with DM. A redn. in vascular  
resistance may be a primary hemodynamic mechanism of the manner in which  
**troglitazone** lowers BP. Insulin **sensitizers** may offer  
potential **therapeutic** advantage in subjects with DM with  
elevated BP.

IT 59112-80-0, C-Peptide

RL: BOC (Biological occurrence); BIOL (Biological study); OCCU  
(Occurrence)

(vasodilating effects of **troglitazone** on blood pressure at  
rest and during mental stress in type 2 **diabetes** mellitus)

L11 ANSWER 9 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:483860 HCAPLUS

DOCUMENT NUMBER: 131:295412

TITLE: Effects of troglitazone on atherogenic lipoprotein  
phenotype in coronary patients with insulin resistance

AUTHOR(S): Sunayama, Satoshi; Watanabe, Yoshiro; Ohmura,  
Hirotoshi; Sawano, Masato; Shimada, Kazunori; Mokuno,  
Hiroshi; Daida, Hiroyuki; Yamaguchi, Hiroshi

CORPORATE SOURCE: Department of Cardiology, Juntendo University, Tokyo,  
Japan

SOURCE: Atherosclerosis (Shannon, Irel.) (1999), 146(1),  
187-193

CODEN: ATHSBL; ISSN: 0021-9150

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Insulin resistance is assocd. with atherogenic lipoprotein phenotype, including small dense LDL particle, hypertriglycemia and low HDL cholesterol levels. **Troglitazone**, a novel **insulin sensitizing** agent, may improve the assocd. lipid profile in patients with insulin resistance. We examd. the effects of **troglitazone** (400 mg daily for 12 wk) in 12 non-diabetic coronary patients (60.+-.10 yr), all of whom had hyperinsulinemic response to an oral glucose load. **Troglitazone** markedly reduced the **insulin** response. After the **treatment**, plasma triglycerides decreased by 32% ( $P < 0.05$ ), HDL cholesterol increased by 11% ( $P < 0.05$ ) and LDL peak particle diam. increased from 24.7.+-.0.3 to 25.5.+-.0.5 nm ( $P < 0.01$ ). These lipidic improvements were assocd. with a significant rise in postheparin lipoprotein lipase levels (175.+-.52 to 217.+-.69 ng/mL,  $P < 0.01$ ). In patients with **insulin** resistance syndrome, **troglitazone** improved the atherogenic lipoprotein phenotype as well as hyperinsulinemia. Our data suggest that **troglitazone therapy** could reduce the atherosclerotic risk due to insulin resistance even in non-diabetic patients.

IT 9004-10-8, **Insulin**, biological studies  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
 (troglitazone effect on atherogenic lipoprotein phenotype in coronary patients with insulin resistance)

L11 ANSWER 10 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:430972 HCAPLUS

DOCUMENT NUMBER: 131:208924

TITLE: Effects of troglitazone on substrate storage and utilization in insulin-resistant rats

AUTHOR(S): Sreenan, Seamus; Keck, Sara; Fuller, Timothy; Cockburn, Brian; Burant, Charles F.

CORPORATE SOURCE: Department of Medicine, The University of Chicago, Chicago, IL, 60637, USA

SOURCE: Am. J. Physiol. (1999), 276(6, Pt. 1), E1119-E1129  
 CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Elevated serum and tissue lipid stores are assocd. with skeletal muscle insulin resistance and diminished glucose-stimulated insulin secretion, the hallmarks of type 2 **diabetes**. We studied the effects of 6-wk **treatment** with the **insulin sensitizer troglitazone** on substrate storage and utilization in lean control and Zucker **diabetic** fatty (ZDF) rats. **Troglitazone** prevented development of **diabetes** and lowered serum triglycerides (TG) in ZDF rats. Soleus muscle glycogen and TG content were elevated twofold in untreated ZDF rats, and both were normalized by **troglitazone** to lean control levels ( $P < 0.05$ ). **Troglitazone** also normalized **insulin**-stimulated glucose uptake as well as basal and insulin stimulated glycogen synthesis, implying increased skeletal muscle glycogen turnover. The proportion of active pyruvate dehydrogenase (PDH) in soleus muscle was reduced in ZDF relative to lean control rat muscle (16.+-.2 vs. 21.+-.2%) but was restored by **troglitazone treatment** (30.+-.3%). Increased PDH activation was assocd. with a 70% increase in glucose oxidn. Muscle lipoprotein lipase activity was decreased by 35% in ZDF compared with lean control rats and was increased twofold by **troglitazone**. Palmitate oxidn. and incorporation into TG were higher in ZDF relative to lean control rats but were unaffected by **troglitazone treatment**. **Troglitazone** decreased the incorporation of glucose into the acyl group of TG by 60% in ZDF rats. In summary, ZDF rats demonstrate increased skeletal muscle glycogen and TG stores, both of which were reduced by **troglitazone treatment**. **Troglitazone** appears to increase both glycogen and TG turnover in skeletal muscle. Normalization of PDH activity and decreased glucose incorporation into acyl TG may underlie the improvements in intracellular



substrate utilization and energy stores, which lead to decreased serum TG and glucose.

L11 ANSWER 11 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:396319 HCAPLUS

DOCUMENT NUMBER: 131:208944

TITLE: Troglitazone inhibits voltage-dependent calcium currents in guinea pig cardiac myocytes

AUTHOR(S): Nakajima, Toshiaki; Iwasawa, Kuniaki; Oonuma, Hitoshi; Imuta, Hiroyuki; Hazama, Hisanori; Asano, Michiko; Morita, Toshihiro; Nakamura, Fumitaka; Suzuki, Jun-Ichi; Suzuki, Seiji; Kawakami, Yasushi; Omata, Masao; Okuda, Yukichi

CORPORATE SOURCE: Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Ibaraki, Japan

SOURCE: Circulation (1999), 99(22), 2942-2950

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It has been suggested that intracellular Ca<sup>2+</sup> overload in cardiac myocytes leads to the development of **diabetic** cardiomyopathy.

**Troglitazone**, an **insulin-sensitizing** agent, is a promising **therapeutic** agent for **diabetes** and has been shown to prevent **diabetes**-induced myocardial changes. To elucidate the underlying mechanism of **troglitazone** action on cardiac myocytes, the effects of **troglitazone** on voltage-dependent Ca<sup>2+</sup> currents were examd. and compared with classic Ca<sup>2+</sup> antagonists (verapamil and nifedipine). Whole-cell voltage-clamp techniques were applied in single guinea pig atrial myocytes. Under control conditions with CsCl internal soln., the voltage-dependent Ca<sup>2+</sup> currents consisted of both T-type (ICa,T) and L-type (ICa,L) Ca<sup>2+</sup> currents. **Troglitazone** effectively reduced the amplitude of ICa,L in a concn.-dependent manner. **Troglitazone** also suppressed ICa,T, but the effect of **troglitazone** on ICa,T was less potent than that on ICa,L. The current-voltage relationships for ICa,L and the reversal potential for ICa,L were not altered by **troglitazone**. The half-maximal inhibitory concn. of **troglitazone** on ICa,L measured at a holding potential of -40 mV was 6.3 .mu.mol/L, and 30 .mu.mol/L **troglitazone** almost completely inhibited ICa,L. **Troglitazone** 10 .mu.mol/L did not affect the time courses for inactivation of ICa,L and inhibited ICa,L mainly in a use-independent fashion, without shifting the voltage-dependency of inactivation. This effect was different from those of verapamil and nifedipine. **Troglitazone** also reduced isoproterenol- or cAMP-enhanced ICa,L. These results demonstrate that **troglitazone** inhibits voltage-dependent Ca<sup>2+</sup> currents (T-type and L-type) and then antagonizes the effects of isoproterenol in cardiac myocytes, thus possibly playing a role in preventing **diabetes**-induced intracellular Ca<sup>2+</sup> overload and subsequent myocardial changes.

L11 ANSWER 12 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:372266 HCAPLUS

DOCUMENT NUMBER: 131:69224

TITLE: Down regulation of peroxisome proliferator-activated receptor .gamma. expression by inflammatory cytokines and its reversal by thiazolidinediones

AUTHOR(S): Tanaka, T.; Itoh, H.; Doi, K.; Fukunaga, Y.; Hosoda, K.; Shintani, M.; Yamashita, J.; Chun, T.-H.; Inoue, M.; Masatsugu, K.; Sawada, N.; Saito, T.; Inoue, G.; Nishimura, H.; Yoshimasa, Y.; Nakao, K.

CORPORATE SOURCE: Department Medicine Clinical Science, Graduate School Medicine, Kyoto Univ., Kyoto, 606, Japan

SOURCE: Diabetologia (1999), 42(6), 702-710

CODEN: DBTGAI; ISSN: 0012-186X

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous studies show that inflammatory cytokines play a part in the development of insulin resistance. Thiazolidinediones were developed as insulin-**sensitizing drugs** and are ligands for the peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.). The authors hypothesized that the anti-**diabetic** mechanism of thiazolidinediones depends on the quantity of PPAR.gamma. in the insulin resistant state in which inflammatory cytokines play a part. The authors isolated rat PPAR.gamma.1 and .gamma.2 cDNAs and examd. effects of various cytokines and thiazolidinediones on PPAR.gamma. mRNA expression in rat mature adipocytes. Various inflammatory cytokines, such as tumor necrosis factor-.alpha. (TNF-.alpha.), interleukin(IL)-1.alpha., IL-1.beta., IL-6, and leukemia inhibitory factor decreased PPARy mRNA expression. H2O2, lysophosphatidylcholine, or phorbol 12-myristate 13-acetate also decreased the expression of PPAR.gamma.. The suppression of PPAR.gamma. mRNA expression caused by 10 nmol/L TNF-.alpha. was reversed 60% and 55% by 10<sup>-4</sup> mol/L **troglitazone** and 10<sup>-4</sup> mol/L of **pioglitazone**, resp. The suppression of glucose transporter 4 mRNA expression caused by TNF-.alpha. was also reversed by thiazolidinediones. Assocd. with the change of PPAR.gamma. mRNA expression, **troglitazone** improved glucose uptake suppressed by TNF-.alpha.. This study suggests that inflammatory cytokines could be factors that regulate PPAR.gamma. expression for possible modulation of insulin resistance. The authors speculate that the regulation of PPAR.gamma. mRNA expression may contribute to the anti-**diabetic** mechanism of thiazolidinediones.

L11 ANSWER 13 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:338839 HCAPLUS

DOCUMENT NUMBER: 131:139297

TITLE: Does metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats?

AUTHOR(S): Katayama, Shigehiro; Kosegawa, Itaru

CORPORATE SOURCE: The Fourth Department of Medicine, Saitama Medical School, Saitama, 350-0495, Japan

SOURCE: Obes. NIDDM (1999), 209-214. Editor(s): Shima, Kenji. Elsevier: Amsterdam, Neth.

CODEN: 67RKA2

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Insulin resistance has been given much attention in relation to the pathogenesis of essential hypertension as well as non-insulin-dependent **diabetes** mellitus (NIDDM) and obesity. This chapter summarizes effects of hypoglycemic agents such as sulfonylurea, biguanide or the newly developed **insulin sensitizer** such as **troglitazone**, on blood pressure and presents our investigation of their hypotensive effects in an animal model of NIDDM assocd. with insulin resistance, Otsuka Long-Evans Tokushima Fatty (OLETF) rats. In our study, blood pressure increased with age, reaching 160 mmHg at 23 wk. Although metformin, **troglitazone** and glibenclamide improved glucose tolerance, the former two, but not glibenclamide, lowered blood pressure in OLETF rats. Metformin and **troglitazone** also diminished plasma triglyceride levels. Plasma membrane GLUT4 protein content was significantly augmented 1.48 times with **treatment** with glibenclamide and 1.32-2.0 times with administration of metformin. Plasma norepinephrine and epinephrine concns. were lower in the **treated** group than those in controls. These results suggest that metformin and **troglitazone**, but not glibenclamide, lower blood pressure in animal models of insulin resistance, giving further evidence for insulin **sensitizing** hypoglycemic agents' beneficial effect on blood pressure.

IT 9004-10-8, Insulin, biological studies .

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(metformin or **troglitazone** ameliorate insulin

resistance and lower blood pressure in OLETF rats)

IT **97322-87-7, Troglitazone**  
 RL: BAC (Biological activity or effector, except adverse); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (metformin or **troglitazone** ameliorate **insulin**  
 resistance and lower blood pressure in OLETF rats)

L11 ANSWER 14 OF 60 HCAPLUS COPYRIGHT 1999 ACS  
 ACCESSION NUMBER: 1999:289426 HCAPLUS  
 DOCUMENT NUMBER: 130:320852  
 TITLE: Composition, food product and uses of  
 3-guanidinopropionic acid  
 INVENTOR(S): Meglasson, Martin D.  
 PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA  
 SOURCE: U.S., 9 pp., Cont.-in-part of U.S. Ser. No. 751,239.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5900435	A	19990504	US 1994-196250	19940224
WO 9303724	A1	19930304	WO 1992-US6776	19920819
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 1991-750559	19910826
			US 1991-751239	19910826
			WO 1992-US6776	19920819

AB The present invention provides a new compn., food product and uses for a known compd. More particularly, the present invention provides a new pharmaceutical compn. contg. 3-guanidinopropionic acid (I) and a method of using I to prevent or **treat** obesity in non-insulin dependent **diabetic** (NIDDM) patients that is caused by **treatment** with anti-**diabetic drugs**, such as an insulin-**sensitizing drug** or an insulin secretion stimulating **drug**. Examples of **insulin sensitizing drugs** are **pioglitazone** and **pioglitazone** hydrochloride. Examples of insulin secretion stimulating **drugs** are glyburide and glimepiride. The present invention also provides a new food product contg. I and a method of using I to increase endurance, stamina and exercise capacity. I was administered to obese **diabetic** mice that were **treated** with **pioglitazone** hydrochloride; I antagonized in a dose-dependent manner the wt. gain. Combination of I and **pioglitazone** did not impair the anti-**diabetic** action of the insulin **sensitizer**. This indicates that I is of benefit in preventing or **treating** the obesity that results from use of an anti-**diabetic drug** by selectively blocking its undesirable obesity-promoting action without affecting its desirable anti-hyperglycemic action.

L11 ANSWER 15 OF 60 HCAPLUS COPYRIGHT 1999 ACS  
 ACCESSION NUMBER: 1999:284669 HCAPLUS  
 DOCUMENT NUMBER: 131:111226  
 TITLE: Troglitazone and metformin, but not glibenclamide,  
 decrease blood pressure in Otsuka long Evans Tokushima  
 fatty rats  
 AUTHOR(S): Kosegawa, Itaru; Chen, Sufang; Awata, Takuya; Negishi,  
 Kiyohiko; Katayama, Shigehiro  
 CORPORATE SOURCE: The Fourth Department of Medicine, Saitama Medical  
 School, Saitama, 350-04, Japan  
 SOURCE: Clin. Exp. Hypertens. (1999), 21(3), 199-211

CODEN: CEHYER; ISSN: 1064-1963  
PUBLISHER: Marcel Dekker, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB To det. whether hypoglycemic agents such as sulfonylureas, biguanides and the newly developed **insulin sensitizers** such as **troglitazone**, have hypotensive effects in an animal model of non-insulin-dependent **diabetes mellitus** assocd. with insulin resistance, male Otsuka Long Evans Tokushima Fatty (OLETF) rats aged 12 wk were administered following hypoglycemic agents or vehicle by gavage for 26 wk; glibenclamide (5 mg/kg/day), metformin (100 mg/kg/day) and **troglitazone** (70 mg/kg/day). The gain in body wt. was similar in the different groups. At 36 wk of age, **troglitazone** significantly decreased fasting plasma glucose levels when compared to controls. The area under the curve (AUC) for insulin during glucose loading (2g/kg, i.p.) was 50% lower in the group **treated** with **troglitazone**. Serum triglyceride levels in **troglitazone** -**treated** rats were also significantly lower than in the glibenclamide-**treated** group. Plasma membrane GLUT4 protein content was significantly augmented by a factor of 1.48-fold ( $p < 0.02$ ) in the glibenclamide-**treated** group and tended to be increased 1.32 times by administration of metformin ( $p = 0.06$ ). The systolic blood pressure increased with age in controls and the glibenclamide-**treated** group. In contrast, **treatment** with either metformin or **troglitazone** significantly decreased systolic blood pressure after the age of 29 wk. Plasma norepinephrine and epinephrine concns. did not show a significant decrease in the **treated** group when compared with the control group. These results suggest that metformin and **troglitazone**, but not glibenclamide, lower blood pressure in an animal model of insulin resistance, providing further evidence of the beneficial effect of insulin **sensitizing** hypoglycemic agents on blood pressure.

IT 97322-87-7, Troglitazone

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(**insulin sensitizing** hypoglycemic agents effect on  
blood pressure)

L11 ANSWER 16 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:284562 HCAPLUS

DOCUMENT NUMBER: 130:320683

TITLE: Effect of troglitazone on plasma lipid metabolism and lipoprotein lipase

AUTHOR(S): Kobayashi, Junji; Nagashima, Izumi; Hikita, Minoru;  
Bujo, Hideaki; Takahashi, Kazuo; Otabe, Masako;  
Morisaki, Nobuhiro; Saito, Yasushi

CORPORATE SOURCE: Second Department of Internal Medicine, Chiba  
University School of Medicine and Health Sciences  
Center, Chiba University, Chiba City, 260-0856, Japan

SOURCE: Br. J. Clin. Pharmacol. (1999), 47(4), 433-439  
CODEN: BCPHBM; ISSN: 0306-5251

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To clarify how **troglitazone**, an **insulin-sensitizing** agent, affects lipid metab. and postheparin plasma lipoprotein lipase (LPL). Fifteen patients (3 male, 12 female) (the av. age 62. $\pm$ .7 yr; the mean body mass index (BMI) 25. $\pm$ .3 kg/m<sup>2</sup>) were recruited for this study. The serum lipids and postheparin plasma lipoprotein lipase (LPL) mass before and 4 wk after oral administration of **troglitazone** (200 mg day<sup>-1</sup>) were measured. A mouse preadipocyte cell line, 3T3-L1, was incubated with **troglitazone** and LPL enzyme protein mass in the culture media was measured by an enzyme linked immunosorbent assay. A reverse transcription polymerase chain reaction (RT-PCR) using primers specific for the carboxyl terminal 135 amino acid of mouse LPL cDNA was used to evaluate the effect of **troglitazone**

on expression of LPL and Northern blot anal. carried out to det. expression of LPL. The av. levels before **treatment** of fasting serum total cholesterol, triglycerides, high d. lipoprotein cholesterol, plasma glucose and glycoHb Alc were 5.6. $\pm$ .0.9, 1.8. $\pm$ .1.0, 1.5. $\pm$ .0.5, 8.1. $\pm$ .1.7 mmol l<sup>-1</sup> and 7.8. $\pm$ .1.6% resp. Four weeks after **treatment**, those levels were 5.4. $\pm$ .0.9, 1.2. $\pm$ .0.3 (P=0.004), 1.6. $\pm$ .0.5 (P=0.02) mmol l<sup>-1</sup>, 7.7. $\pm$ .2.3 mmol l<sup>-1</sup> and 7.3. $\pm$ .0.6% (P=0.01), resp. The postheparin plasma LPL mass increased from 226. $\pm$ .39 to 257. $\pm$ .68 ng ml<sup>-1</sup> (P=0.03) during that period. The LPL mass in the media of 3T3 L1 cells cultured in the presence of 10, 20 or 30 .mu.M of this compd. increased in a dose dependent manner. RT-PCR revealed that the area of the bands of the RT-PCR products on 1.5% agarose gel analyzed with NIH image from the cell exts. cultured in the presence of 10 .mu.M **troglitazone** was significantly larger (P=0.0069) than that in the absence of this compd. Northern blot anal. revealed that in the cultured 3T3-L1 cells, the expression of LPL was enhanced in the presence of 10 .mu.M **troglitazone**. **Troglitazone** improves plasma triglyceride-rich lipoproteins metab. by enhancing the expression of LPL in adipocytes.

L11 ANSWER 17 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:150053 HCAPLUS

DOCUMENT NUMBER: 130:261325

TITLE: The emerging role of thiazolidinediones in the **treatment of diabetes-mellitus** and related disorders

AUTHOR(S): Subramaniam, S.

CORPORATE SOURCE: Dr. Reddy's Research Foundation, Hyderabad, India

SOURCE: Clin. Exp. Hypertens. (1999), 21(1 & 2), 121-136

CODEN: CEHYER; ISSN: 1064-1963

PUBLISHER: Marcel Dekker, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 37 refs. Type II **diabetes** is a polygenic disorder, characterized in most cases by early onset of resistance to the action of insulin. Insulin **sensitizers** belonging to the thiazolidinedione class offer the first **therapeutic** option specifically targeting the underlying insulin resistance. **Troglitazone** is the prototype **drug** of this class and has been approved for marketing in several countries. **Troglitazone** offers several benefits over traditional oral hypoglycemic agents such as sulfonylureas and the biguanide metformin. Most of these advantages are related to better control of glycemic parameters with **troglitazone** alone or when added to existing **treatment**. In addn., it has interesting lipid lowering activity that may be of potential benefit in reducing morbidity from cardiovascular disease among **diabetics**. However, **troglitazone** may not be the ideal **insulin sensitizer** since 20-30% of **diabetics** do not respond to it. Also, it produces liver toxicity in 2% of patients, necessitating withdrawal of the **drug**. A no. of second generation insulin **sensitizers**, belonging to the same chem. class as **troglitazone**, are in clin. development. The role of insulin **sensitizers** in the management of **diabetes** and other diseases in which insulin resistance is an underlying feature, is likely to undergo evolution as more information is obtained from clin. studies.

L11 ANSWER 18 OF 60. HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:133149 HCAPLUS

DOCUMENT NUMBER: 130:336064

TITLE: Complementary measures for promoting insulin sensitivity in skeletal muscle

AUTHOR(S): McCarty, M. F.

CORPORATE SOURCE: Nutrition 21, San Diego, CA, 92109, USA

SOURCE: Med. Hypotheses (1998), 51(6), 451-464

CODEN: MEHYDY; ISSN: 0306-9877

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 193 refs. Insulin resistance of skeletal muscle is fundamental to both syndrome X and its frequent sequel, type II **diabetes**. In these disorders, excessive exposure of muscle to free fatty acids (FFAs) and their metabolic derivs. appears to play a prominent role in the induction of insulin resistance. Recent evidence suggests that activation of novel isoforms of protein kinase C (PKC) by diacylglycerol may mediate at least part of the adverse impact of FFAs on muscle insulin sensitivity. Vitamin E and fish oil omega-3s, by promoting the activity of diacylglycerol kinase and inhibiting that of phosphatidate phosphohydrolase, should reduce diacylglycerol levels, thus accounting for their documented favorable impact on insulin sensitivity. Thiazolidinediones such as **troglitazone**, on the other hand, appear to intervene in the signaling pathway whereby PKC down-regulates insulin function. The **insulin-sensitizing** activity of **chromium picolinate** may be attributable, at least in part, to increased expression of insulin receptors. In combination with lifestyle modifications which reduce FFA exposure - wt. loss, very-low-fat eating, excessive training - these measures can be expected to work in a complementary way to promote increased nos. of insulin receptors that are more functionally competent. As these measures appear to be safe and well-tolerated, they may have utility for the prevention of **diabetes** as well as its **therapy**. When they do not prove sufficient to achieve optimal glycemic control, excessive hepatic glucose output and impaired cell response to glucose can be addressed with metformin and sulfonylureas, resp. The prospects for a rational medical management of type II **diabetes**, obviating the need for injectable insulin, have never been brighter.

L11 ANSWER 19 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:81573 HCAPLUS

DOCUMENT NUMBER: 130:134187

TITLE: **Treatment of diabetes** with insulin sensitizer thiazolidinedione and insulin secretagogue sulfonylurea

INVENTOR(S): Buckingham, Robin Edwin; Smith, Stephen Alistair

PATENT ASSIGNEE(S): Smithkline Beecham PLC, UK

SOURCE: PCT Int. Appl., 19 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9903476	A1	19990128	WO 1998-GB2109	19980716
W:				
AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:				
GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9884487	A1	19990210	AU 1998-84487	19980716
PRIORITY APPLN. INFO.:			GB 1997-15306	19970718
			WO 1998-GB2109	19980716

AB A method for the **treatment** of **diabetes** mellitus and conditions assocd. with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amt. of an insulin sensitizer and a sub-maximal amt. of an insulin secretagogue, to a mammal in need thereof; and a pharmaceutical compn. for use in such method are disclosed. The insulin secretagogue is esp. sulfonylurea. The insulin sensitizer is esp. 5-[4-[2-(N-methyl-N-(2-

pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (I). Tablet formulations contg. I maleate are given.

IT 97322-87-7, Troglitazone 111025-46-8,  
Pioglitazone 122320-73-4

RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(as **insulin sensitizer**; **treatment** of

**diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue sulfonylurea)

IT 155141-29-0

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(tablet contg.; **treatment** of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue sulfonylurea)

L11 ANSWER 20 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:9697 HCAPLUS

DOCUMENT NUMBER: 130:61089

TITLE: **Treatment** of **diabetes** with thiazolidinedione and metformin

INVENTOR(S): Smith, Stephen Alistair

PATENT ASSIGNEE(S): Smithkline Beecham Plc, UK

SOURCE: PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9857634	A1	19981223	WO 1998-EP3690	19980615
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9885393	A1	19990104	AU 1998-85393	19980615
PRIORITY APPLN. INFO.:			GB 1997-12857	19970618
			GB 1998-6706	19980327
			WO 1998-EP3690	19980615

AB A method for the **treatment** and/or prophylaxis of **diabetes** mellitus, conditions assocd. with **diabetes** mellitus, and certain complications thereof, in a mammal which method comprises administering an effective nontoxic and pharmaceutically acceptable amt. of an insulin sensitizer rosiglitazone (I) and a biguanide antihyperglycemic agent such as metformin. Pharmacokinetics of I and metformin administered alone or in combination are described. Formulations for prep. tablets contg. I is presented.

IT 97322-87-7, Troglitazone 111025-46-8,

Pioglitazone 155141-29-0, Rosiglitazone maleate

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**treatment** of **diabetes** with thiazolidinedione **insulin sensitizer** and metformin)

L11 ANSWER 21 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:8339 HCAPLUS

DOCUMENT NUMBER: 130:47350

TITLE: Beneficial effect of long-term combined **treatment** with voglibose and pioglitazone on pancreatic islet function of genetically **diabetic** GK rats

AUTHOR(S): Ishida, Hitoshi; Kato, S.; Nishimura, M.; Mizuno, N.;  
Fujimoto, S.; Mukai, E.; Kajikawa, M.; Yamada, Y.;  
Odaka, H.; Ikeda, H.; Seino, Y.

CORPORATE SOURCE: Dep. Metabolism Clinical Nutrition, School Medicine,  
Kyoto Univ., Kyoto, Japan

SOURCE: Horm. Metab. Res. (1998), 30(11), 673-678  
CODEN: HMMRA2; ISSN: 0018-5043

PUBLISHER: Georg Thieme Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Effects of voglibose (an  $\alpha$ -glucosidase inhibitor) and  
**pioglitazone** (an **insulin sensitizer**) on  
glycemic control and on the function of pancreatic islets were evaluated  
using Goto-Kakizaki (GK) rats with non-insulin-dependent **diabetes**  
mellitus (NIDDM). Five week administration (8-13 wk of age in GK rats) of  
voglibose alone (added to the chow at a concn. of 10 ppm),  
**pioglitazone** alone (10 mg/kg daily p.o.), or both of the agents  
together improved fasting blood plasma glucose levels and those at 120 min  
in oral glucose tolerance tests. Insulin secretory capacity in response  
to glucose of the isolated islets, assessed by batch incubation, was  
improved in the voglibose and in the voglibose plus **pioglitazone**  
groups. Eight-week administration (5-13 wk of age) of voglibose and  
voglibose plus **pioglitazone** successfully lowered the fasting  
levels of plasma glucose and triglyceride. The glucose-responsiveness in  
insulin release from the islets was also recovered by the **therapy**  
. The **treatment** increased the insulin content of the islets to  
almost twice that in untreated controls. Thus, **treatment** by  
these **drugs** can not only effectively ameliorate the metabolic  
derangement of NIDDM in GK rats, but it can also restore the deteriorated  
islet function, possibly through protection from glucose toxicity.

L11 ANSWER 22 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:805567 HCAPLUS

DOCUMENT NUMBER: 130:163039

TITLE: Thiazolidinediones and insulin resistance: peroxisome  
proliferator-activated receptor  $\gamma$  activation  
stimulates expression of the CAP gene

AUTHOR(S): Ribon, Vered; Johnson, John H.; Camp, Heidi S.;  
Saltiel, Alan R.

CORPORATE SOURCE: Department of Physiology, University of Michigan  
School of Medicine, Ann Arbor, MI, 48109, USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(25),  
14751-14756  
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB C-Cbl-assocd. protein (CAP) is a signaling protein that interacts with  
both c-Cbl and the insulin receptor that may be involved in the specific  
insulin-stimulated tyrosine phosphorylation of c-Cbl. The restricted  
expression of CAP in cells metabolically sensitive to insulin suggests an  
important potential role in insulin action. The expression of CAP mRNA  
and proteins are increased in 3T3-L1 adipocytes by the insulin  
**sensitizing** thiazolidinedione **drugs**, which are  
activators of the peroxisome proliferator-activated receptor  $\gamma$ .  
(PPAR $\gamma$ ). The stimulation of CAP expression by PPAR $\gamma$ .  
activators results from increased transcription. This increased  
expression of CAP was accompanied by a potentiation of insulin-stimulated  
c-Cbl tyrosine phosphorylation. Administration of the thiazolidinedione  
**troglitazone** to Zucker (fa/fa) rats markedly increased the  
expression of the major CAP isoform in adipose tissue. This effect was  
sustained for 12 wk of **treatment** and accompanied the  
ability of **troglitazone** to prevent the onset of **diabetes**  
and its complications. Thus, CAP is the first PPAR $\gamma$ -sensitive gene  
identified that participates in insulin signaling and may play a role in  
thiazolidinedione-induced insulin **sensitization**.



## IT 97322-87-7, Troglitazone

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(thiazolidinediones and **insulin** resistance in relation to  
peroxisome proliferator-activated receptor .gamma. activation  
stimulation expression of CAP gene and **diabetes** prevention)

L11 ANSWER 23 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:696182 HCAPLUS

DOCUMENT NUMBER: 130:47348

TITLE: In vivo effects of pioglitazone on uncoupling  
protein-2 and -3 mRNA levels in skeletal muscle of  
hyperglycemic KK miceAUTHOR(S): Shimokawa, Teruhiko; Kato, Miyuki; Watanabe, Yuka;  
Hirayama, Reiko; Kurosaki, Eiji; Shikama, Hisataka;  
Hashimoto, SeiichiCORPORATE SOURCE: Molecular Medicine Laboratories, Institute for Drug  
Discovery Research, Yamanouchi Pharmaceutical Co.,  
Ltd., Tsukuba, 305-8585, JapanSOURCE: Biochem. Biophys. Res. Commun. (1998), 251(1), 374-378  
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Pioglitazone** is a thiazolidinedione **drug** (TZD) which  
potently and specifically stimulates peroxisome proliferator-activated  
receptor .gamma. (PPAR .gamma.) and **sensitizes** cells to insulin.  
Since TZDs are thought to increase energy expenditure, changes in  
mitochondrial thermogenesis uncoupling protein-2 and -3 mRNA levels in  
response to **pioglitazone treatment** were measured in  
mouse skeletal muscle. Normally hyperglycemic and  
**hyperinsulinemic** KK/Ta mice were given **pioglitazone** for  
2 wk to **treat** this non-insulin dependent **diabetes**-like  
condition. During **treatment**, UCP2 mRNA levels increased to 185%  
of normal untreated control levels in soleus muscle. In contrast, UCP3  
mRNA levels significantly decreased, up to 67% of normal untreated control  
levels. Interestingly, UCP3 mRNA levels correlated quite strongly with  
blood glucose levels, with  $r = 0.82$  for gastrocnemius tissue and  $r = 0.92$   
for soleus tissue. These results may indicate that **pioglitazone**  
increases glucose catabolism by direct upregulation of muscle UCP2 gene  
expression in vivo. Therefore, UCP3 gene expression is controlled by a  
different mechanism than UCP2 expression. (c) 1998 Academic Press.

L11 ANSWER 24 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:593691 HCAPLUS

DOCUMENT NUMBER: 130:20453

TITLE: **Troglitazone** prevents **insulin**  
dependent **diabetes** in the non-obese  
**diabetic** mouseAUTHOR(S): Beales, Philip E.; Liddi, Roberto; Giorgini, Angela  
E.; Signore, Alberto; Procaccini, Enrica; Batchelor,  
Kenneth; Pozzilli, PaoloCORPORATE SOURCE: Department of Diabetes and Metabolism, St.  
Bartholomew's Hospital, London, EC1A 7BE, UKSOURCE: Eur. J. Pharmacol. (1998), 357(2/3), 221-225  
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Troglitazone** has recently been introduced in the  
**treatment** of Type 2 **diabetes**. In addn. to its anti-  
**diabetic** effects it acts as a perioxosome proliferator activated  
receptor-gamma (PPAR-.gamma.) agonist and has anti-inflammatory properties  
by inhibiting macrophage tumor necrosis factor-alpha (TNF-.alpha.)  
secretion. It also inhibits the prodn. of endothelial selectin  
(e-selectin). **Troglitazone** also reduces interleukin-1.alpha.

induced nitric oxide prodn. in pancreatic beta-cells, which may be relevant in preventing nitric oxide mediated damage to these cells in the Type 1 **diabetes** process. We tested **troglitazone** in the spontaneous model of autoimmune **diabetes**, the non-obese **diabetic** (NOD) mouse, to det. its effect on the disease process. When administered by gavage from weaning at a dose of 400 mg/kg body wt. (n=32), **troglitazone** reduced the incidence of **diabetes** by 16 wk compared to controls (n=32) in a pattern that was maintained up to the conclusion of the expt. at 31 wk of age (p<0.05). Insulinitis was unaltered (index=1.05.+-.0.71 vs. 1.13.+-.0.82, **treated** vs. controls, p=0.78). The study was repeated using **troglitazone** in the diet of NOD mice (n=24) to give a dose of approx. 200 mg/kg body wt. in order to provide a more consistent level of **troglitazone** during the time course of the expt. There was a redn. of **diabetes** incidence in this group but it did not reach significance. Insulin levels were reduced in gavage **treated** mice although such redn. did not reach significance (p<0.07). We conclude that, in view of its effect on this model of autoimmune **diabetes** and because of its known function as an **insulin sensitizer**, **troglitazone** might be considered for potential use in those patients with Type 1 masquerading as Type 2 **diabetes**.

IT 97322-87-7, **Troglitazone**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**troglitazone** prevents **insulin** dependent **diabetes** in the non-obese **diabetic** mouse)

L11 ANSWER 25 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:531781 HCAPLUS

DOCUMENT NUMBER: 129:239715

TITLE: Troglitazone effects on gene expression in human skeletal muscle of type II **diabetes** involved up-regulation of peroxisome proliferator-activated receptor-.gamma.

AUTHOR(S): Park, Kyong Soo; Ciaraldi, Theodore P.; Lindgren, Kristin; Abrams-Carter, Leslie; Mudaliar, Sunder; Nikoulina, Svetlana E.; Tufari, Sherrie R.; Veerkamp, Jacques H.; Vidal-Puig, Antonio; Henry, Robert R.  
CORPORATE SOURCE: Dep. Med., Univ. California, San Diego, La Jolla, CA, 92093, USA

SOURCE: J. Clin. Endocrinol. Metab. (1998), 83(8), 2830-2835  
CODEN: JCEMAZ; ISSN: 0021-972X

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Troglitazone**, besides improving **insulin** action in **insulin**-resistant subjects, is also a specific ligand for the nuclear receptor peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.). To det. whether **troglitazone** might enhance **insulin** action by stimulation of PPAR.gamma. gene expression in muscle, total PPAR.gamma. mRNA, and protein were detd. in skeletal muscle cultures from **nondiabetic** control and type II **diabetic** subjects before and after **treatment** of cultures with **troglitazone** (4 days .+-. **troglitazone**, 11.5 .mu.M). **Troglitazone treatment** increased PPAR.gamma. mRNA levels up to 3-fold in muscle cultures from type II **diabetics** (277.+-.63 to 630.+-.100 .times. 103 copies/.mu.g total RNA, P = 0.003) and in **nondiabetic** control subjects (200.+-.42 to 490.+-.81, P = 0.003). PPAR.gamma. protein levels in both **diabetic** (4.7.+-.1.6 to 13.6.+-.3.0 AU/10 .mu.g protein, P < 0.02) and **nondiabetic** cells (7.4.+-.1.0 to 12.7.+-.1.8, P < 0.05) were also up-regulated by **troglitazone treatment**. Increased PPAR.gamma. was assocd. with stimulation of human adipocyte lipid binding protein (ALBP) and muscle fatty acid binding protein (mFABP) mRNA, without change in the mRNA for glycerol-3-phosphate dehydrogenase, PPAR.delta., myogenin, uncoupling protein-2, or sarcomeric .alpha.-actin protein. In summary, we

showed that **troglitazone** markedly induces PPAR. $\gamma$ ., ALBP, and mFABP mRNA abundance in muscle cultures from both **nondiabetic** and type II **diabetic** subjects. Increased expression of PPAR. $\gamma$ . protein and other genes involved in glucose and lipid metab. in skeletal muscle may account, in part, for the **insulin sensitizing** effects of **troglitazone** in type II **diabetes**.

IT 9004-10-8, **Insulin**, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(**sensitization**; **troglitazone** effects on gene expression in human skeletal muscle of type II **diabetes** involved up-regulation of peroxisome proliferator-activated receptor- $\gamma$ .)

L11 ANSWER 26 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:454369 HCAPLUS

DOCUMENT NUMBER: 129:170355

TITLE: Effects of **troglitazone** on hepatic and peripheral **insulin** resistance induced by growth hormone excess in rats

AUTHOR(S): Sugimoto, Miyuki; Takeda, Noriyuki; Nakashima, Kazuya; Okumura, Shoji; Takami, Kazuhisa; Yoshino, Kouji; Hattori, Junko; Ishimori, Masatoshi; Takami, Rieko; Sasaki, Akihiko; Yasuda, Keigo

CORPORATE SOURCE: Third Department of Internal Medicine, Gifu University School of Medicine, Gifu, 500, Japan

SOURCE: Metab., Clin. Exp. (1998), 47(7), 783-787

CODEN: METAJ; ISSN: 0026-0495

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This work sought to clarify whether **troglitazone**, a new **insulin-sensitizing drug** of the thiazolidinedione class, counteracts the insulin-antagonistic effects of recombinant human growth hormone (rhGH) on glucose metab. in rats. Male Wistar rats were **treated** with either rhGH or rhGH plus **troglitazone**. RhGH (20 IU/kg/day) was given s.c. twice daily for 2 days. **Troglitazone** was given at 100 mg/kg/day orally for 5 days before and during the 2 days of rhGH. Euglycemic clamp studies with an insulin infusion rate of 8 mU/kg/min were performed in these rats after an overnight fast. Hepatic glucose output (HGO), glucose infusion rate (GIR), and glucose disappearance rate (GDR) were measured. Fasting levels of plasma glucose, insulin and free fatty acids were comparable among rats **treated** with rhGH, rhGH plus **troglitazone**, and controls. Basal HGO was also comparable among the 3 groups. HGO was suppressed during the hyperinsulinemic glucose clamp in control rats, but not in rhGH-**treated** rats. When **troglitazone** was coadministered with rhGH, the suppression of HGO during the glucose clamp was comparable to that of controls. GIR and GDR were decreased by rhGH **treatment** compared with control values. They returned to normal levels in rats **treated** with both rhGH and **troglitazone**. Apparently, rhGH **treatment** impaired insulin's ability to suppress HGO and stimulate peripheral glucose utilization. **Troglitazone** blocks the **insulin-antagonistic** effects of GH on HGO and peripheral glucose utilization.

IT 97322-87-7, **Troglitazone**

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(hepatic and peripheral **insulin** resistance induced by growth hormone excess response to)

IT 9004-10-8, **Insulin**, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)

(**troglitazone** effect on hepatic and peripheral **insulin** resistance induced by growth hormone excess)

L11 ANSWER 27 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:320318 HCAPLUS  
DOCUMENT NUMBER: 129:62740  
TITLE: Troglitazone: an **antidiabetic** agent  
AUTHOR(S): Chen, Connie  
CORPORATE SOURCE: University HealthSystem Consortium, Oak Brook, IL,  
60523, USA  
SOURCE: Am. J. Health-Syst. Pharm. (1998), 55(9), 905-925  
CODEN: AHSPEK; ISSN: 1079-2082  
PUBLISHER: American Society of Health-System Pharmacists  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The pharmacol., pharmacokinetics, clin. efficacy, adverse effects, and dosage and administration of **troglitazone** are reviewed. **Troglitazone** is the first oral thiazolidinedione approved for use in **treating** non-insulin-dependent **diabetes** mellitus (NIDDM). The **drug's** mechanism of action has not been fully elucidated. **Troglitazone** acts as an **insulin sensitizer**. Cell-line and animal models indicate that **troglitazone** may decrease hepatic glucose output by decreasing the rate of gluconeogenesis in the liver or by increasing glycolysis. **Troglitazone** is rapidly absorbed after oral administration, with peak concn. occurring in two to three hours. Food increases absorption by 30-85%. The **drug** is extensively metabolized in the liver. **Troglitazone** has been shown to be efficacious in **treating** NIDDM, both as monotherapy and in combination with oral sulfonylureas. Patients who are obese or who have high fasting plasma insulin levels may derive the greatest benefit. Patients with impaired glucose tolerance, syndrome X, polycystic ovary syndrome, gestational **diabetes**, or Werner's syndrome may also benefit from **troglitazone**. Adverse effects, including hematol. abnormalities, liver toxicity, and hypoglycemia, have been rare in published trials; no life-threatening effects have been reported thus far. The recommended initial dosage is 200 mg once daily with meals, with an increase to 400 mg daily if satisfactory glycemic control is not achieved after two to four weeks. The av. wholesale price is \$348 for 100 200-mg tablets and \$534 for 100 400-mg tablets. **Troglitazone** may be an effective agent for **treating** NIDDM, esp. in patients who are obese or who have high fasting plasma insulin levels.

L11 ANSWER 28 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:319335 HCAPLUS  
DOCUMENT NUMBER: 129:62668  
TITLE: Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 **diabetes**  
AUTHOR(S): Minamikawa, Jun; Tanaka, Satsuki; Yamauchi, Mika; Inoue, Daisuke; Koshiyama, Hiroyuki  
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Internal Medicine, Hyogo Prefectural Amagasaki Hospital, Hyogo, 660-0828, Japan  
SOURCE: J. Clin. Endocrinol. Metab. (1998), 83(5), 1818-1820  
CODEN: JCEMAZ; ISSN: 0021-972X  
PUBLISHER: Endocrine Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB There is increasing evidence that insulin resistance may be causally related to atherosclerosis. The measurement of common carotid arterial intimal and medial complex thickness (IMT) by B-mode ultrasound technique has been recognized as a powerful and non-invasive method to evaluate early atherosclerotic lesions. We investigated the effect of **treatment** with **troglitazone**, an **insulin sensitizer**, on IMT in a total of 135 Japanese subjects with type 2 **diabetes**. **Troglitazone** (400 mg daily) was administered for 6 mo in 57 patients. Compared to control group (n=78), the group given **troglitazone** showed a significant decrease in IMT as early as 3 mo after the administration (IMT change: -0.080[SE 0.016] mm vs.

control 0.027[SE 0.007] mm,  $P < 0.001$ ). The decrease in IMT was also found after 6 mo, although further decrease was not obsd. Both HbA1c and postprandial serum triglycerides were decreased after **troglitazone**, but there was no statistically significant relation between a decrease in IMT and those in HbA1c or postprandial triglycerides. These findings indicate that **troglitazone** has a potent inhibitory effect on progression of early atherosclerotic lesions probably through the decreased insulin resistance in type 2 **diabetes**.

L11 ANSWER 29 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:319302 HCAPLUS

DOCUMENT NUMBER: 129:49491

TITLE: Troglitazone regulation of glucose metabolism in human skeletal muscle cultures from obese type II **diabetic** subjects

AUTHOR(S): Park, Kyong Soo; Ciaraldi, Theodore P.; Abrams-Carter, Leslie; Mudaliar, Sunder; Nikoulina, Svetlana E.; Henry, Robert R.

CORPORATE SOURCE: Department of Medicine, University of California-San Diego, La Jolla, CA, 92093, USA

SOURCE: J. Clin. Endocrinol. Metab. (1998), 83(5), 1636-1643  
CODEN: JCEMAZ; ISSN: 0021-972X

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To det. the effects of **troglitazone** on abnormal skeletal muscle glucose metab., muscle cultures from type II **diabetic** patients were grown for 4-6 wk and then fused for 4 days either without or with **troglitazone** (1-5  $\mu\text{g/mL}$ ; chronic studies) or had **troglitazone** added for 90 min (1-5  $\mu\text{g/mL}$ ) at completion of fusion (acute studies). Acute **troglitazone treatment** stimulated glucose uptake, but not glycogen synthase (GS) activity 2-fold ( $P < 0.05$ ) in a dose-dependent fashion and to the same extent as the addn. of maximal (33 nmol/L) insulin. Maximal chronic **troglitazone** (5  $\mu\text{g/mL}$  for 4 days) increased both glucose uptake (from  $9.0 \pm 1.5$  to  $40.9 \pm 8.1$  pmol/mg protein.cntdot.min;  $P < 0.05$ ) and GS fractional velocity (from  $5.4 \pm 0.7\%$  to  $20.6 \pm 6.3\%$ ;  $P < 0.05$ ) by approx. 4-fold. At each concn. of chronic **troglitazone**, glucose uptake rates were similar in the absence and presence of maximal (33 nmol/L) insulin concns. In contrast, insulin-stimulated GS activity was greater ( $P < 0.05$ ) when maximal chronic **troglitazone** and acute **insulin** were combined than when chronic **troglitazone** alone was used. After 4 days of **troglitazone**, GLUT1 mRNA and protein increased about 2-fold ( $P < 0.05$ ) without a change in GLUT4 or GS mRNA and protein. We conclude that **troglitazone** has both acute and chronic effects to improve skeletal muscle glucose metab. of obese type II **diabetic** subjects. These effects involve direct insulin mimetic stimulatory actions as well as indirect insulin-sensitizing properties.

IT 9004-10-8, **Insulin**, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**troglitazone** regulation of glucose metab. in human skeletal muscle cultures from obese type II **diabetic** subjects)

L11 ANSWER 30 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:282662 HCAPLUS

DOCUMENT NUMBER: 128:293552

TITLE: Insulin-induced vasodilatation and endothelial function in obesity/**insulin** resistance.  
Effects of **troglitazone**

AUTHOR(S): Tack, C. J. J.; Ong, M. K. E.; Lutterman, J. A.; Smits, P.

CORPORATE SOURCE: Department Internal Medicine, Division General Internal Medicine, University Nijmegen, Nijmegen, 6500 HB, Neth.

SOURCE: Diabetologia (1998), 41(5), 569-576

CODEN: DBTG AJ; ISSN: 0012-186X  
PUBLISHER: Springer-Verlag  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Insulin resistance is assocd. with a decreased vasodilator response to insulin. Because insulin's vasodilator effect is NO dependent, this impairment may reflect endothelial dysfunction. **Troglitazone**, an **insulin-sensitizer**, might thus improve insulin-dependent and/or endothelium-dependent vascular function in insulin resistant obese subjects. For 8 wk, obese subjects were **treated** with either 400 mg **troglitazone** once daily or placebo. At the end of each **treatment** period, the authors measured forearm vasodilator responses (plethysmog.) to intraarterial administered acetylcholine and Na nitroprusside; insulin sensitivity and insulin-induced vascular and neurohumoral responses (clamp); vasoconstrictor responses to NG-monomethyl-L-arginine (L-NMMA) during hyperinsulinemia; and ambulatory 24-h blood pressure (ABPM). Baseline data (placebo) of obese subjects were compared with those obtained in lean control subjects. Obese subjects were insulin resistant compared with leans (whole-body glucose uptake: 26.8 vs. 53.9  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ ). **Troglitazone** improved whole-body glucose uptake (to 31.9  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ ), and forearm glucose uptake (from 1.09 to 2.31  $\mu\text{mol dL}^{-1} \text{min}^{-1}$ ). Insulin-induced vasodilatation was blunted in obese subjects (% increase in forearm blood flow (FBF) in lean 66.5%, vs. 10.1% in obese), but did not improve during **troglitazone**. Vascular responses to acetylcholine, Na nitroprusside and L-NMMA did not differ between the obese and lean group, nor between both **treatment** periods in the obese individuals. In conclusion, in insulin resistant obese subjects, endothelial vascular function is normal despite impaired vasodilator responses to insulin. **Troglitazone** improved **insulin** sensitivity but it had no effects on endothelium-dependent and -independent vascular responses. These data do not support an assocn. between insulin resistance and endothelial function.

IT 97322-87-7, **Troglitazone**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**troglitazone** effect on **insulin**-induced vasodilatation and endothelial function in obesity/insulin resistance)

L11 ANSWER 31 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:269208 HCAPLUS

DOCUMENT NUMBER: 128:252819

TITLE: Novel Euglycemic and Hypolipidemic Agents. 1

AUTHOR(S): Lohray, Braj B.; Bhushan, Vidya; Rao, Bheema P.; Madhavan, Gurram R.; Murali, Nagabelli; Rao, Krovvidi N.; Reddy, Ananth K.; Rajesh, Bagepalli M.; Reddy, Pamulapati G.; Chakrabarti, Ranjan; Vikramadithyan, Reeba K.; Rajagopalan, Ramanujam; Mamidi, Rao N. V. S.; Jajoo, Hemant K.; Subramaniam, Swaminathan

CORPORATE SOURCE: Medicinal and Organic Chemistry Pharmacology and Clinical Research, Dr. Reddy's Research Foundation, Hyderabad, 500 050, India

SOURCE: J. Med. Chem. (1998), 41(10), 1619-1630

CODEN: JMC MAR; ISSN: 0022-2623

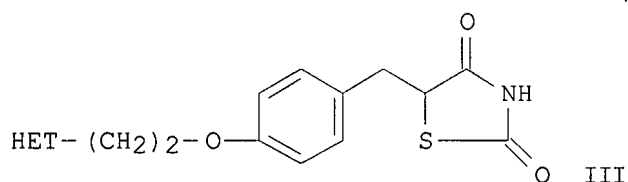
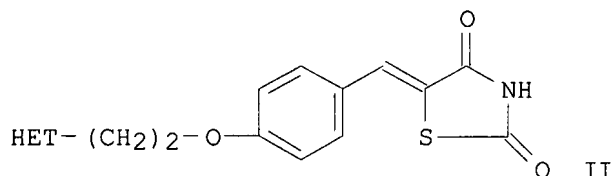
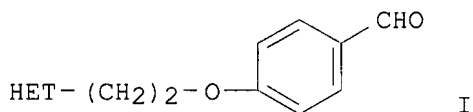
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 128:252819

GI



AB A series of [[(heterocyclyl)ethoxy]benzyl]-2,4-thiazolidinediones have been synthesized by the condensation of corresponding aldehyde I (HET = heterocyclyl) and 2,4-thiazolidinedione followed by hydrogenation. Both unsatd. thiazolidinedione II and its satd. counterpart III have shown antihyperglycemic activity. Many of these compds. have shown superior euglycemic and hypolipidemic activity compared to **troglitazone** (CS 045). The indole analog DRF-2189 [HET = Q] was a very potent **insulin sensitizer**, comparable to **BRL-49653** in genetically obese C57BL/6J-ob/ob and 57BL/KsJ-db/db mice. Pharmacokinetic and tissue distribution studies conducted on **BRL-49653** and DRF-2189 that these **drugs** are well-distributed in target tissues. On the basis of euglycemic activity as well as enhanced selectivity against redn. of triglycerides in plasma, DRF-2189 has been selected for further evaluation.

L11 ANSWER 32 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:262812 HCAPLUS

DOCUMENT NUMBER: 128:316828

TITLE: Insulin sensitizing agents and polycystic ovary syndrome

AUTHOR(S): Pasquali, Renato; Filicori, Marco

CORPORATE SOURCE: Division of Endocrinology, Department of Internal Medicine, University of Bologna, Bologna, I-40138, Italy

SOURCE: Eur. J. Endocrinol. (1998), 138(3), 253-254

CODEN: EJOEEP; ISSN: 0804-4643

PUBLISHER: BioScientifica

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 16 refs. This commentary reviews studies of the benefits of **insulin sensitizing** agents, metformin and **troglitazone** in particular, in reducing **hyperinsulinemia** in women with obesity and PCOS.

L11 ANSWER 33 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:225433 HCAPLUS

DOCUMENT NUMBER: 129:407

TITLE: **BRL 49653** blocks the lipolytic actions of tumor necrosis factor- $\alpha$ : A potential new **insulin-sensitizing** mechanism for thiazolidinediones

AUTHOR(S): Souza, Sandra C.; Yamamoto, Mia T.; Franciosa, Mark D.; Lien, Ping; Greenberg, Andrew S.  
CORPORATE SOURCE: Jean Mayer Human Nutrition Research Center on Aging, Tufts University, Boston, MA, 02111, USA  
SOURCE: Diabetes (1998), 47(4), 691-695  
CODEN: DIAEAZ; ISSN: 0012-1797  
PUBLISHER: American Diabetes Association  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Thiazolidinediones (TZDs) such as BRL 49653 are a class of **antidiabetic** agents that are agonists for the peroxisome proliferator-activated nuclear receptor (PPAR-.gamma.2). In vivo, TZDs reduce circulating levels of free fatty acids (FFAs) and ameliorate insulin resistance in individuals with obesity and NIDDM. Adipocyte prodn. of TNF-.alpha. is proposed to play a role in the development of **insulin** resistance, and because **BRL 49653** has been shown to antagonize some of the effects of TNF-.alpha., we examd. the effects of TNF-.alpha. and BRL 49653 on adipocyte lipolysis. After a 24-h incubation of TNF-.alpha. (10 ng/mL) with 3T3-L1 adipocytes, glycerol release increased by .apprx.7-fold, and FFA release increased by .apprx.44-fold. BRL 49653 (10 .mu.mol/l) reduced TNF-.alpha.-induced glycerol release by .apprx.50% (P < 0.001) and FFA release by .apprx.90% (P < 0.001). BRL 49653 also reduced glycerol release by .apprx.50% in adipocytes pretreated for 24 h with TNF-.alpha.. Prolonged **treatment** (5 days) with either BRL 49653 or another PPAR-.gamma.2 agonist, 15-d-.DELTA.-12,14-prostaglandin J2 (15-d.DELTA.PGJ2), blocked TNF-.alpha.-induced glycerol release by .apprx.100%. Catecholamine (isoproterenol)-stimulated lipolysis was unaffected by BRL 49653 and 15-d.DELTA.PGJ2. BRL 49653 partially blocked the TNF-.alpha.-mediated redn. in protein levels of hormone-sensitive lipase and perilipin A, two proteins involved in adipocyte lipolysis. These data suggest a novel pathway that may contribute to the ability of the TZDs to reduce serum FFA and increase insulin sensitivity.

IT **122320-73-4, BRL 49653**

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(**BRL 49653** blocks the lipolytic actions of tumor necrosis factor-.alpha.: a potential new insulin-**sensitizing** mechanism for thiazolidinediones)

IT **9004-10-8, Insulin**, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(**BRL 49653** blocks the lipolytic actions of tumor necrosis factor-.alpha.: a potential new insulin-**sensitizing** mechanism for thiazolidinediones)

L11 ANSWER 34 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:163855 HCAPLUS

DOCUMENT NUMBER: 128:213122

TITLE: Effects of **troglitazone** on hepatic and peripheral **insulin** resistance induced by GH excess in rats

AUTHOR(S): Sugimoto, Miyuki; Takeda, Noriyuki; Nakashima, Kazuya; Okumura, Shoji; Yoshino, Kouji; Takami, Kazuhisa; Hattori, Junko; Ishimori, Masatoshi; Takami, Rieko; Sasaki, Akihiko; Yasuda, Keigo

CORPORATE SOURCE: Sch. Med., Gifu Univ., Gifu, 500, Japan

SOURCE: Gifu Daigaku Igakubu Kiyo (1998), 46(1), 14-19

CODEN: GDIKAN; ISSN: 0072-4521

PUBLISHER: Gifu Daigaku Igakubu

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB It is well known that short-term growth hormone administration in humans and animals induces insulin resistance and glucose intolerance. The purpose of the present study was to clarify whether **troglitazone**, a new **insulin sensitizing drug** of the thiazolidinedione class, counteracts the insulin antagonistic effects of



recombinant human growth hormone (rhGH) on glucose metab. in rats. Male Wistar rats weighing 184 g go 226 g were **treated** either with rhGH (n = 8) or rhGH plus **troglitazone** (n = 8). RhGH (20 IU/kg of BW/day) was given by s.c. injection twice daily for 2 days. **Troglitazone** was given po 20 mg/day for 5 days preceding and 2 days along with rhGH. Saline was injected to the control rats (n = 7). Euglycemic clamp studies with insulin infusion rate of 8 mU/kg/min were carried out in these rats after an overnight fast. Hepatic glucose output (HGO), glucose infusion rate (GIR), and glucose disappearance rate (GDR) were measured. Fasting levels of plasma glucose (6.6. $\pm$ .0.1, 6.1. $\pm$ .0.3, 6.5. $\pm$ .0.2 mmol/L), insulin (187.5. $\pm$ .24.1, 206.4. $\pm$ .24.1, 182.3. $\pm$ .31.0 pmol/L), and serum free fatty acid (1.58. $\pm$ .0.18, 1.43. $\pm$ .0.16, 1.61. $\pm$ .0.25 mEq/L) were comparable among the rats **treated** with rhGH, rhGH plus **troglitazone**, and the controls. Basal hepatic glucose output was also comparable among the 3 **treatment** groups. HGO was suppressed significantly during the hyperinsulinemic glucose clamp in the control rats but not in the rats **treated** with rhGH **treatment**. When **troglitazone** was coadministered with rhGH, suppressibility of HGO during the glucose clamp was restored. The GIR (13.5. $\pm$ .4.5 vs. 24.1. $\pm$ .4.1 mg/kg/min) and GDR (18.1. $\pm$ .5.8 vs. 30.3. $\pm$ .5.2 mg/kg/min) were decreased by the rhGH **treatment** compared with the control values. They returned to the normal levels in the rats **treated** with both rhGH and **troglitazone** (GIR; 22.4. $\pm$ .5., GDR; 24.7. $\pm$ .7.1). From these results, it is evident that rhGH **treatment** produced hepatic and peripheral insulin resistance. **Troglitazone treatment** could almost completely prevent the rhGH-induced insulin resistance.

IT 9004-10-8, Insulin, biological studies

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(effects of **troglitazone** on hepatic and peripheral insulin resistance induced by GH excess in rats)

L11 ANSWER 35 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:105775 HCAPLUS

DOCUMENT NUMBER: 128:225448

TITLE: Mechanisms of insulin resistance and new pharmacological approaches to metabolism and **diabetic** complications

AUTHOR(S): Donnelly, Richard; Qu, Xianqin

CORPORATE SOURCE: Department of Pharmacology, University of Sydney, New South Wales, Australia

SOURCE: Clin. Exp. Pharmacol. Physiol. (1998), 25(2), 79-87  
CODEN: CEXPB9; ISSN: 0305-1870

PUBLISHER: Blackwell Science Pty Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 85 refs. Resistance to insulin-mediated glucose transport and metab. has been identified as a primary mechanism in the pathogenesis of non-insulin-dependent **diabetes** mellitus (NIDDM) and as a target for **drug** development. The etiol. of insulin resistance is likely to be multifactorial, but the present review focuses on candidate post-receptor mechanisms of insulin resistance, particularly protein kinase C (PKC), and the metabolic and genetic significance of .beta.3-adrenoceptors (.beta.3-AR) in adipose tissue. Multiple lines of evidence suggest that isoform-selective activation of PKC phosphorylates and down-regulates one or more substrates involved in glucose transport and metab. (e.g., glycogen synthase and the insulin receptor) and recent studies have shown increased expression of calcium-independent isoenzymes (PKC-.epsilon. and PKC-.theta.) in the membrane fraction of skeletal muscle in fructose- and fat-fed rat models of insulin resistance. In addn., there is sep. evidence that glucose-induced PKC activation plays an important role in the micro- and macrovascular complications of **diabetes**. New pharmacol. approaches to NIDDM and obesity have focused on **insulin-sensitizing** agents (e.g. **troglitazone**), .beta.3-AR agonists, antilipolytic **drugs**

(e.g. the adenosine A1 receptor agonist GR 79236) and selective inhibitors of PKC isoforms (e.g. the inhibitor of PKC-.beta. LY 333531). Exptl. studies with GR 79236 show that this **drug** ameliorates the hypertriglyceridemia induced by fructose feeding and that the redn. in fatty acid levels is assocd. with secondary improvements in glucose tolerance. Recent insights into the pathogenesis of NIDDM and its assocd. complications have been used to develop a range of new **therapeutic** agents that are currently showing promise in clin. and preclin. development.

L11 ANSWER 36 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:102221 HCAPLUS

DOCUMENT NUMBER: 128:213309

TITLE: Metabolic effects of troglitazone monotherapy in type 2 **diabetes** mellitus: a randomized, double-blind, placebo-controlled trial

AUTHOR(S): Maggs, David G.; Buchanan, Thomas A.; Burant, Charles F.; Cline, Gary; Gumbiner, Barry; Hsueh, Willa A.; Inzucchi, Silvio; Kelley, David; Nolan, John; Olefsky, Jerrold M.; Polonsky, Kenneth S.; Silver, David; Valiquett, Thomas R.; Shulman, Gerald I.

CORPORATE SOURCE: Yale University, New Haven, CT, USA

SOURCE: Ann. Intern. Med. (1998), 128(3), 176-185

CODEN: AIMEAS; ISSN: 0003-4819

PUBLISHER: American College of Physicians

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Troglitazone** is a new **insulin-sensitizing** agent used to **treat** type 2 **diabetes** mellitus. The mechanism by which **troglitazone** exerts its effect on systemic glucose metab. is unknown. To det. the effects of 6 mo of **troglitazone** monotherapy on glucose metab. in patients with type 2 **diabetes** mellitus. Randomized, double-blind, placebo-controlled trial. Six general clin. research centers at university hospitals. 93 Patients (mean age, 52 yr) with type 2 **diabetes** mellitus (mean fasting plasma glucose level, 11.2 mmol/L) who were being **treated** with diet alone or who had discontinued oral **antidiabetic** medication **therapy**. Patients were randomly assigned to one of five **treatment** groups (100, 200, 400, or 600 mg of **troglitazone** daily or placebo) and had metabolic assessment before and after 6 mo of **treatment**. Plasma glucose and insulin profiles during a meal tolerance test; basal hepatic glucose prodn. and insulin-stimulated glucose disposal rate during a hyperinsulinemic-euglycemic clamp procedure. **Troglitazone** at 400 and 600 mg/d decreased both fasting and postprandial plasma glucose levels by approx. 20%. All four **troglitazone** dosages also decreased fasting and postprandial triglyceride levels; 600 mg of the **drug** per day decreased fasting free fatty acid levels. Plasma insulin levels decreased in the 200-, 400-, and 600-mg/d groups, and C-peptide levels decreased in all five study groups. Basal hepatic glucose prodn. was suppressed in the 600-mg/d group compared with the placebo group. **Troglitazone** at 400 and 600 mg/d increased glucose disposal rate by approx. 45% above pretreatment levels. Stepwise regression anal. showed that **troglitazone therapy** was the strongest predictor of a decrease in fasting or postprandial glucose levels. Fasting C-peptide level was the next strongest predictor (higher C-peptide level equaled greater glucose-lowering effect). **Troglitazone** monotherapy decreased fasting and postprandial glucose levels in patients with type 2 **diabetes**, primarily by augmenting insulin-mediated glucose disposal.

IT 59112-80-0, C-Peptide

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(metabolic effects of **troglitazone** monotherapy in type 2 **diabetes** mellitus)

L11 ANSWER 37 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:66089 HCAPLUS  
 DOCUMENT NUMBER: 128:149586  
 TITLE: Novel **treatment** of leptin resistance  
 INVENTOR(S): Poste, George Henry; Smith, Stephen Alistair  
 PATENT ASSIGNEE(S): Smithkline Beecham PLC, UK; Poste, George Henry;  
 Smith, Stephen Alistair  
 SOURCE: PCT Int. Appl., 30 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9802159	A1	19980122	WO 1997-GB1928	19970714
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
CA 2260044	AA	19980122	CA 1997-2260044	19970714
AU 9735526	A1	19980209	AU 1997-35526	19970714
EP 921798	A1	19990616	EP 1997-931945	19970714
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI			
CN 1230114	A	19990929	CN 1997-197722	19970714
NO 9900097	A	19990111	NO 1999-97	19990111
PRIORITY APPLN. INFO.:			GB 1996-14740	19960712
			GB 1996-14751	19960712
			GB 1996-16407	19960805
			GB 1996-16409	19960805
			GB 1996-16412	19960805
			WO 1997-GB1928	19970714

OTHER SOURCE(S): MARPAT 128:149586

AB A method for the **treatment** and/or prophylaxis of leptin resistance and/or conditions assocd. with leptin resistance and/or complications thereof, comprises the internal administration of an effective, non-toxic and pharmaceutically acceptable amt. of a leptin **sensitizer** or a pharmaceutically acceptable deriv. thereof.  
 Effects of **insulin sensitizer BRL 49653** on plasma leptin concns. and on fat ob mRNA expression were examd. in high fat-fed and high carbohydrate-fed adult Wistar rats.  
**Treatment** with **BRL 49653** reduced plasma leptin concns. in high fat-fed rats, but not in high carbohydrate-fed rats and there was no difference in ob mRNA expression between high fat-fed and high carbohydrate-fed rats with or without **treatment**.

IT 97322-87-7 111025-46-8 122320-73-4,

**BRL 49653**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (thiazolidinediones as leptin **sensitizers** for **treatment** of leptin resistance)

L11 ANSWER 38 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:628150 HCAPLUS

DOCUMENT NUMBER: 127:287977

TITLE: **Troglitazone** does not **sensitize**  
 the liver to insulin in the normal dog

AUTHOR(S): Balcom, J.; Sindelar, D.; Neal, D.; Cherrington, A. D.

CORPORATE SOURCE: Department of Molecular Physiology & Biophysics,  
 Vanderbilt University School of Medicine, Nashville,  
 TN, USA

SOURCE: Diabetes Res. (1997), 32(3), 115-132  
CODEN: DIREEM; ISSN: 0265-5985  
PUBLISHER: Teviot-Kimpton Publications  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB **Troglitazone** is a novel member of the thiazolidinedione family. These agents have been shown to enhance peripheral insulin sensitivity in animal models of insulin resistance and have been considered as a possible future **treatment** for NIDDM. Little work has been done, however, to examine their effect on hepatic glucose metab. One group (Tr) of dogs (n = 5) was **treated** for two weeks with **troglitazone** (16 mg/kg/day), while another group (C) (n = 5) was **treated** with a placebo. The exptl. protocol, which was carried out in conscious dogs after an overnight fast, consisted of a 120 min tracer equilibration period, a 30 min control period, and two 100 min test periods. A pancreatic clamp was used to control the endocrine pancreas. Insulin and glucagon were infused intraportally at basal rates during the control period. Insulin infusion was increased by 0.2 mU/kg/min in the first test period and was increased to 1.2 mU/kg/min in the second test period. The glucagon infusion rate was not altered. Arterial insulin levels were similar in both groups over the three periods (C: 7  $\pm$  1, 10  $\pm$  1, 27  $\pm$  3; Tr: 8  $\pm$  1, 11  $\pm$  1, 29  $\pm$  3  $\mu$ U/mL). Glucagon levels did not change in either group. Euglycemia existed in the control period and hyperglycemia was brought about during the last two periods (C: 105  $\pm$  4, 162  $\pm$  2, 159  $\pm$  7; Tr: 109  $\pm$  3, 168  $\pm$  3, 163  $\pm$  7 mg/dL). Endogenous glucose prodn. (tracer-detd.) decreased similarly in both groups (C: 2.3  $\pm$  0.2, 1.2  $\pm$  0.5, 0.0  $\pm$  0.3; Tr: 2.2  $\pm$  0.3, 0.9  $\pm$  0.4, 0.0  $\pm$  1.3 mg/kg-min) in the two test periods resp. Net hepatic glucose output ceased in both groups and the liver consumed glucose in the second test period (C: 2.0  $\pm$  0.4, -0.1  $\pm$  0.3, -1.6  $\pm$  0.4; Tr: 1.7  $\pm$  0.2, 0.2  $\pm$  0.2, -0.8  $\pm$  0.3 mg/kg-min). Thus, when used in the manner described, **troglitazone** did not **sensitize** the normal dog liver to the combined effects of hyperglycemia and hyperinsulinemia. This suggests that the **drug** is unlikely to result in unwanted hypoglycemia.

IT **97322-87-7, Troglitazone**

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**troglitazone** does not **sensitize** liver to the combined effects of hyperglycemia and hyperinsulinemia)

IT **9004-10-8, Insulin**, biological studies

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(**troglitazone** does not **sensitize** liver to the combined effects of hyperglycemia and hyperinsulinemia)

L11 ANSWER 39 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:530785 HCAPLUS

DOCUMENT NUMBER: 127:229472

TITLE: The **insulin sensitizer**,

**BRL 49653**, reduces systemic fatty acid supply and utilization and tissue lipid availability in the rat

AUTHOR(S): Oakes, Nicholas D.; Camilleri, Souad; Furler, Stuart M.; Chisholm, Donald J.; Kraegen, Edward W.

CORPORATE SOURCE: Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, NSW 2010, Australia

SOURCE: Metab., Clin. Exp. (1997), 46(8), 935-942  
CODEN: METAJ; ISSN: 0026-0495

PUBLISHER: Saunders

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Thiazolidinediones are oral insulin-**sensitizing** agents that may be useful for the **treatment** of non-insulin-dependent diabetes mellitus (NIDDM). **BRL 49653** ameliorates

**insulin** resistance and improves glucoregulation in high-fat-fed (HF) rats. It is known that thiazolidinediones bind to the peroxisome proliferator-activated receptor (PPAR. $\gamma$ ) in fat cells, but the extent to which the improved glucoregulation and hypolipidemic effects relate to adipose tissue requires clarification. We therefore examd. **BRL 49653** effects on lipid metab. in HF and control (high-starch-fed [HS]) rats. The diet period was 3 wk, with **BRL 49653** (10  $\mu$ .mol/kg/d) or vehicle gavage administered over the last 4 days. Studies were performed on animals in the conscious fasted state. In HF rats, rate consts. governing 3H-palmitate clearance were unaffected by **BRL 49653**. This finding, taken with a concurrent decrease of fasting plasma nonesterified fatty acids (NEFA) ( $P < .01$ , ANOVA), demonstrated that systemic NEFA supply and hence abs. utilization are reduced by **BRL 49653**. Hepatic triglyceride (TG) prodn. (HTGP) assessed using Triton WR1339 was unaffected by diet or **BRL 49653**. In liver, **BRL 49653** increased **insulin**-stimulated conversion of glucose into fatty acid in both HF (by 270%) and HS (by 30%) groups ( $P < .05$ ). Relative to HS rats, HF animals had substantially elevated levels of muscle diglyceride (diacylglycerol [DG] by 240%,  $P < .001$ ). **BRL 49653** significantly reduced muscle DG in HF (by 30%,  $P < .05$ ) but not in HS rats. The agent did not reduce the intake of dietary lipid. In conclusion, these results are consistent with a primary action of **BRL 49653** in adipose tissue to conserve lipid by reducing systemic lipid supply and subsequent utilization. The parallel effects of diet and **BRL 49653 treatment** on **insulin** resistance and muscle acylglyceride levels support the involvement of local lipid oversupply in the generation of muscle insulin resistance.

IT 122320-73-4, **BRL 49653**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**insulin sensitizer BRL 49653**

reduces systemic fatty acid supply and utilization and tissue lipid availability)

IT 9004-10-8, **Insulin**, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(**insulin sensitizer BRL 49653**

reduces systemic fatty acid supply and utilization and tissue lipid availability)

L11 ANSWER 40 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:525406 HCAPLUS

DOCUMENT NUMBER: 127:214951

TITLE: **Treatment** with the oral antidiabetic

agent troglitazone improves  $\beta$  cell responses to glucose in subjects with impaired glucose tolerance  
Cavaghan, Melissa K.; Ehrmann, David A.; Byrne, Maria M.; Polonsky, Kenneth S.

CORPORATE SOURCE: Department of Medicine, The University of Chicago and Pritzker School of Medicine, Chicago, IL, 60637, USA

SOURCE: J. Clin. Invest. (1997), 100(3), 530-537

CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Impaired glucose tolerance (IGT) is assocd. with defects in both insulin secretion and action and carries a high risk for conversion to non-insulin-dependent **diabetes** mellitus (NIDDM).

**Troglitazone**, an **insulin sensitizing** agent, reduces glucose concns. in subjects with NIDDM and IGT but is not known to affect insulin secretion. We sought to det. the role of  $\beta$  cell function in mediating improved glucose tolerance. Obese subjects with IGT received 12 wk of either 400 mg daily of **troglitazone** ( $n = 14$ ) or placebo ( $n = 7$ ) in a randomized, double-blind design. Study measures at baseline and after **treatment** were glucose and insulin

responses to a 75-g oral glucose tolerance test, insulin sensitivity index (SI) assessed by a frequently sampled i.v. glucose tolerance test, insulin secretion rates during a graded glucose infusion, and .beta. cell glucose-sensing ability during an oscillatory glucose infusion.

**Troglitazone** reduced integrated glucose and **insulin** responses to oral glucose by 10% (P = 0.03) and 39% (P = 0.003), resp. SI increased from 1.3+-.0.3 to 2.6+-.0.4 .times. 10-5min-1pM-1 (P = 0.005). Av. insulin secretion rates adjusted for SI over the glucose interval 5-11 mmol/L were increased by 52% (P = 0.02), and the ability of the .beta. cell to entrain to an exogenous oscillatory glucose infusion, as evaluated by anal. of spectral power, was improved by 49% (P = 0.04). No significant changes in these parameters were demonstrated in the placebo group. In addn. to increasing **insulin** sensitivity, we demonstrate that **troglitazone** improves the reduced .beta. cell response to glucose characteristic of subjects with IGT. This appears to be an important factor in the obsd. improvement in glucose tolerance.

IT 9004-10-8, **Insulin**, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(**antidiabetic** agent **troglitazone** improves .beta. cell responses to glucose in humans with impaired glucose tolerance)

L11 ANSWER 41 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:436377 HCAPLUS

DOCUMENT NUMBER: 127:156453

TITLE: Antihypertensive and vasculo- and renoprotective effects of pioglitazone in genetically obese **diabetic** rats

AUTHOR(S): Yoshimoto, Takanobu; Naruse, Mitsuhide; Nishikawa, Megumi; Naruse, Kiyoko; Tanabe, Akiyo; Seki, Toshirou; Imaki, Toshihiro; Demura, Reiko; Aikawa, Eizo; Demura, Hiroshi

CORPORATE SOURCE: Dep. Medicine, Inst. Clinical Endocrinology, Tokyo Women's Medical College, Tokyo, 162, Japan

SOURCE: Am. J. Physiol. (1997), 272(6, Pt. 1), E989-E996  
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Although an improvement of insulin sensitivity has been shown to be a new **therapeutic** approach for **treating diabetes** mellitus, details of effects of this **treatment** on the cardiovascular system and possible renal complications remain unknown. In the present study, we investigated the effects of a thiazolidine deriv., **pioglitazone**, and examd. the **insulin-sensitizing** action on blood pressure, nephropathy, and vascular changes in genetically obese **diabetic** Wistar fatty (WF) rats. **Pioglitazone** (3 mg.cntdot.kg-1.cntdot.day-1) was orally administered for 13 wk starting at the age of 5 wk, and the results were compared with those of vehicle-**treated** WF rats. At the age of 18 wk, vehicle-**treated** WF rats were assocd. with mild hypertension, nephropathy with proteinuria, histol. glomerular injury, and renal arteriosclerosis in addn. to hyperglycemia, hyperinsulinemia, and hyperlipidemia. **Treatment** with **pioglitazone** significantly improved glucose and lipid metab. In addn., it lowered blood pressure, decreased proteinuria, and prevented glomerular injury, renal arteriosclerosis, and aortic medial wall thickening, whereas body wt., food intake, sodium balance, and urinary norepinephrine excretion were significantly increased. These results suggest that the **insulin-sensitizing** agent **pioglitazone** is effective in correcting not only glucose and lipid metab. but also cardiovascular and renal complications in non-insulin-dependent **diabetes** mellitus.

IT 111025-46-8, **Pioglitazone**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(antihypertensive **insulin-sensitizing** agent **pioglitazone** in **treatment** of **diabetes**)

mellitus and cardiovascular and renal complications in NIDDM)

L11 ANSWER 42 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:397042 HCAPLUS

DOCUMENT NUMBER: 127:130789

TITLE: Pioglitazone. In vitro effects on rat hepatoma cells and in vivo liver hypertrophy in KKAY mice

AUTHOR(S): Weinstock, R. S.; Murray, F. T.; Diani, A.; Sangani, G. A.; Wachowski, M. B.; Messina, J. L.

CORPORATE SOURCE: Dep. Medicine Physiology, SUNY Health Science Center, Syracuse, NY, 13210, USA

SOURCE: Pharmacology (1997), 54(4), 169-178

CODEN: PHMGBN; ISSN: 0031-7012

PUBLISHER: Karger

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Pioglitazone** increases **insulin** sensitivity in vivo and in vitro. The effects of this agent on insulin-induced DNA synthesis and hepatic cell growth have not been detd. We examd. the ability of **pioglitazone** to enhance basal and **insulin**-stimulated DNA synthesis in rat H4IIE (H4) hepatoma cells, and to alter liver wt. and histol. in **diabetic** KKAY mice. **Treatment** of H4 cells with increasing concns. of **pioglitazone** for 30 h increased basal DNA synthesis 1.6- to 1.8-fold. With **pioglitazone** pretreatment and submaximal **insulin** concns., DNA synthesis was significantly increased from 2.1-fold (insulin 10-12 mol/l alone) to 3.9-fold ( **insulin** 10-12 mol/l + **pioglitazone** 10-6 mol/l). At maximal concns. of insulin, the enhancement of DNA synthesis increased from 7.4-fold (insulin 10-8 mol/l alone) to 16.2-fold (**insulin** 10-8 mol/l + **pioglitazone** 10-6 mol/l). Glyburide did not increase basal or insulin-stimulated DNA synthesis. In **diabetic** KKAY mice, serum glucose levels decreased and body wt., liver wt. and liver wt. as a percentage of body wt. increased following **pioglitazone treatment**. Histol. studies demonstrated marked hepatocyte distension. The findings suggest that **pioglitazone** acts as an **insulin sensitizer** in rat hepatoma cells, increasing basal and insulin-stimulated DNA synthesis, and stimulating fat synthesis and liver hypertrophy in **diabetic** KKAY mice.

L11 ANSWER 43 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:286116 HCAPLUS

DOCUMENT NUMBER: 126:325298

TITLE: **Antidiabetic** efficacy of **BRL**

**49653**, a potent orally active **insulin -sensitizing** agent, assessed in the C57BL/KsJ db/db **diabetic** mouse by noninvasive [1H]NMR studies of urine

AUTHOR(S): Connor, S. C.; Hughes, M. G.; Moore, G.; Lister, C. A.; Smith, S. A.

CORPORATE SOURCE: SmithKline Beecham Pharmaceuticals, Essex, CM19 5AW, UK

SOURCE: J. Pharm. Pharmacol. (1997), 49(3), 336-344

CODEN: JPPMAB; ISSN: 0022-3573

PUBLISHER: Royal Pharmaceutical Society of Great Britain

DOCUMENT TYPE: Journal

LANGUAGE: English

AB [1H]NMR anal. of urine was used to monitor the efficacy of **BRL 49653** following oral administration for .ltoreq.36 wk to the genetically **diabetic** C57BL/KsJ db/db mouse. The effects of **BRL 49653** on carbohydrate and fatty acid metab. were monitored by detn. of changes in the concns. of low-mol.-wt. urinary metabolites. A qual. comparison of the NMR spectra of urine from untreated **diabetic** mice with those of lean littermates and literature data revealed several abnormalities, the majority of which could be explained in terms of the non-insulin-dependent **diabetes** syndrome exhibited by these

animals. Quant., the most prominent was the extreme glycosuria of both young (8-12 wk) and older (42 wk) **diabetic** mice. This was accompanied by the excretion of a no. of unassigned sugar derivs. and by ketone bodies. Administration of BRL 49653 (3 .mu.mol/kg/day) to db/db mice for 24 days reduced blood glucose concns. to values comparable with those of **nondiabetic** lean littermates and reduced glycosuria by >90%. BRL 49653 reduced excretion of unassigned sugars, acetate, lactate, and the ketone bodies acetoacetate, 3-D-hydroxybutyrate and acetone. The **antidiabetic** efficacy of BRL 49653, assessed from the pattern of urinary metabolites, was maintained over a 36-wk **treatment** period. These results demonstrate the value of [1H]NMR for evaluating noninvasively the efficacy of novel **therapeutic** agents.

L11 ANSWER 44 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:216920 HCAPLUS

DOCUMENT NUMBER: 126:301622

TITLE: Troglitazone reduces contraction by inhibition of vascular smooth muscle cell Ca<sup>2+</sup> currents and not endothelial nitric oxide production

AUTHOR(S): Song, Jianben; Walsh, Mary F.; Igwe, Robert; Ram, Jeffrey L.; Barazi, Mohamad; Dominguez, Ligia J.; Sowers, James R.

CORPORATE SOURCE: Departments of Medicine and Physiology, and Veterans Affairs Medical center, Wayne State University, Detroit, MI, 48201, USA

SOURCE: Diabetes (1997), 46(4), 659-664  
CODEN: DIAEAZ; ISSN: 0012-1797

PUBLISHER: American Diabetes Association, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The **insulin-sensitizing** compd. **troglitazone**

has evolved into a promising **therapeutic** agent for type II **diabetes**. It improves insulin sensitivity and lipoprotein metabolic profiles and lowers blood pressure in humans and rodents. Because **troglitazone** has **insulin-like** effects on a no. of tissues, the authors hypothesized that it may reduce vascular tone through stimulation of endothelial-derived nitric oxide (NO) prodn. or by diminution of vascular smooth muscle cell (VSMC) intracellular calcium ([Ca<sup>2+</sup>]<sub>i</sub>). The results show that **troglitazone** decreases norepinephrine-induced contractile responses in the rat tail artery, an effect not reversed by the NO inhibitor L-nitroarginine Me ester (L-NAME). In contrast, **troglitazone** significantly inhibited L-type Ca<sup>2+</sup> currents in freshly dissocd. rat tail artery and aortic VSMCs and in cultured VSMCs. The data suggest that **troglitazone** attenuates vascular contractility via a mechanism involving VSMC [Ca<sup>2+</sup>]<sub>i</sub> but independent from endothelial generation of NO. Because insulin has been shown to affect vascular tone by both of these mechanisms, **troglitazone** only partially mimics **insulin** action in this tissue.

IT 9004-10-8, **Insulin**, biological studies

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(**troglitazone** reduces contraction by inhibition of vascular smooth muscle cell Ca<sup>2+</sup> currents and not endothelial nitric oxide prodn. in relation to **insulin-sensitizing** activity)

IT 97322-87-7, **Troglitazone**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**troglitazone** reduces contraction by inhibition of vascular smooth muscle cell Ca<sup>2+</sup> currents and not endothelial nitric oxide prodn. in relation to **insulin-sensitizing** activity)

L11 ANSWER 45 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:185513 HCAPLUS

DOCUMENT NUMBER: 126:258926

TITLE: **Antidiabetic** actions of insulin sensitizer



alone or in combination with .alpha.-glucosidase inhibitor in genetically obese-**diabetic** rats, Wistar fatty

AUTHOR(S): Odaka, Hiroyuki; Sano, Yoko; Amano, Nobuyuki; Ikeda, Hitoshi

CORPORATE SOURCE: Pharmaceutical Res. Lab. II, Takeda Chemical Industries Ltd., Japan

SOURCE: Yakuri to Chiryo (1997), 25(2), 355-361  
CODEN: YACHDS; ISSN: 0386-3603

PUBLISHER: Raifu Saiensu Shuppan K.K.

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB The **antidiabetic** actions of **insulin sensitizer**, **pioglitazone.cntdot.HCl**, or **troglitazone**, alone or in combination with .alpha.-glucosidase inhibitor, voglibose, were investigated in genetically obese-**diabetic** rats, Wistar fatty. Fourteen to 19-wk-old, male Wistar fatty rats were orally administered with **pioglitazone.cntdot.HCl** (1 mg/kg/day) or **troglitazone** (30 mg/kg/day) alone or in combination with voglibose (5 ppm) for 14 days. Fatty rats showed hyperglycemia and hypertriglyceridemia; both plasma glucose and triglyceride levels were over 350 mg/dL. **Pioglitazone.cntdot.HCl** decreased plasma glucose and triglyceride to the level 61 and 45% of control, resp. Voglibose was less effective on these plasma components. However, when combined with **pioglitazone.cntdot.HCl** voglibose normalized the plasma glucose level (41% of control, 144 mg/dL) and markedly decreased plasma triglyceride level (33% of control, 120 mg/dL). On the other hand, **troglitazone** showed less effect on plasma glucose (78% of control) and triglyceride (69% of control) levels. **Troglitazone** in combination with voglibose, however, markedly decreased plasma glucose to the level 48% of control, but did not induce a further decrease in plasma triglyceride. An oral glucose tolerance test performed on day 15 revealed that the glucose intolerance in fatty rats was not improved by **pioglitazone.cntdot.HCl** or **troglitazone** alone, but was markedly ameliorated by the combined **treatment** with voglibose. These results indicate that the combined **treatment** of **pioglitazone.cntdot.HCl** with voglibose shows the most potent effect to suppress hyperglycemia and to improve glucose intolerance in wistar fatty rats. On the other hand, **antidiabetic** activity of **troglitazone** which is 1/30 or less than that of **pioglitazone.cntdot.HCl** is also enhanced by the combination with voglibose in fatty rats.

L11 ANSWER 46 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:7888 HCAPLUS

DOCUMENT NUMBER: 126:99145

TITLE: The thiazolidinedione **insulin**

**sensitizer, BRL 49653,**

increases the expression of PPAR-.gamma. and aP2 in adipose tissue of high-fat-fed rats

AUTHOR(S): Pearson, S. L.; Cawthorne, M. A.; Clapham, J. C.; Dunmore, S. J.; Holmes, S. D.; Moore, G. B. T.; Smith, S. A.; Tadayyon, M.

CORPORATE SOURCE: Clore Lab., Univ. Buckingham, Buckinghamshire, MK18 1EG, UK

SOURCE: Biochem. Biophys. Res. Commun. (1996), 229(3), 752-757  
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of the thiazolidinedione **insulin sensitizer BRL 49653** on plasma leptin concns. and on epididymal fat OB, PPAR-.gamma. and aP2 mRNA expression were examd. in high-fat-fed and high-carbohydrate-fed adult Wistar rats. Diets were given for 4 wk, with **BRL 49653** (10 .mu.mol/kg/day) administered by oral gavage for the last 4 days. **Treatment** with **BRL**

**49653** reduced plasma leptin concns. in high-fat-fed rats from 2.34. $\pm$ .0.19 to 1.42. $\pm$ .0.09 ng/mL. Plasma leptin was unaffected by **BRL 49653** in the high-carbohydrate-fed rats. There was no difference in OB mRNA expression between high-fat-fed and high-carbohydrate-fed rats, with or without **treatment**. PPAR- $\gamma$ . and aP2 mRNA expression were significantly increased in the high-fat-fed rats **treated** with **BRL 49653** (and resp.), but not in carbohydrate-fed rats.

IT **122320-73-4, BRL 49653**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (thiazolidinedione **insulin sensitizer, BRL 49653**, increases expression of PPAR- $\gamma$ . and aP2 in adipose tissue of high-fat-fed rats)

L11 ANSWER 47 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1996:735369 HCAPLUS

DOCUMENT NUMBER: 126:42528

TITLE: Troglitazone attenuates high-glucose-induced abnormalities in relaxation and intracellular calcium in rat ventricular myocytes

AUTHOR(S): Ren, Jun; Dominguez, Ligia J.; Sowers, James R.; Davidoff, Amy J.

CORPORATE SOURCE: Dep. Int. Med., Wayne State Univ. Sch. Med., Detroit, MI, USA

SOURCE: Diabetes (1996), 45(12), 1822-1825

CODEN: DIAEAZ; ISSN: 0012-1797

PUBLISHER: American Diabetes Association, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Diabetes** is assocd. with impaired cardiac diastolic dysfunction. Isolated ventricular myocytes from **diabetic** animals demonstrate impaired relaxation concomitant with prolonged intracellular Ca<sup>2+</sup> transients. We have recently shown that maintaining normal adult rat ventricular myocytes in a "**diabetic-like**" culture medium (low insulin and high glucose) produces abnormalities in excitation-contraction coupling similar to in vivo **diabetes**. **Troglitazone** (TRO), a novel **insulin-sensitizing** agent, significantly lower blood pressure and modestly increases cardiac output in vivo, but its direct impact on cardiac function is unknown. To det. whether TRO could prevent high-glucose-induced dysfunction, normal myocytes were maintained in culture for 1-2 days in either normal medium contg. 5 mmol/l glucose or high-glucose medium contg. 25 mmol/l glucose. TRO (5  $\mu$ mol/l) was added to both normal and high-glucose media. Mech. properties were evaluated using a high-resoln. video-edge detection system, and Ca<sup>2+</sup> transients were recorded in fura-2-loaded myocytes. Relaxation from peak contraction was significantly longer in myocytes cultured in high glucose. **Treating** cells with TrO either attenuated or prevented the high-glucose effects, without changing the mech. properties of myocytes cultured in normal medium. TRO also prevented the abnormally slow rates of Ca<sup>2+</sup> transient decay induced by high glucose. Collectively, these data demonstrate that TRO can protect against the high-glucose-induced relaxation defects, perhaps through changes in intracellular Ca<sup>2+</sup> handling. If TRO has both vasodilatory actions and beneficial cardiac properties (e.g., improvement of diastolic function) in the presence of hyperglycemia, this **antidiabetic** agent may prove to have significant salutary cardiovascular effects in type II **diabetes**.

L11 ANSWER 48 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1996:665020 HCAPLUS

DOCUMENT NUMBER: 125:316922

TITLE: Troglitazone enhances differentiation, basal glucose uptake, and Glut1 protein levels in 3T3-L1 adipocytes

AUTHOR(S): Tafuri, Sherrie R.

CORPORATE SOURCE: Dep. Cell Biology, Warner-Lambert Co., Ann Arbor, MI,

48105, USA  
SOURCE: Endocrinology (1996), 137(11), 4706-4712  
CODEN: ENDOAO; ISSN: 0013-7227  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB **Troglitazone** is a member of the thiazolidinedione class of compds., which act as insulin-**sensitizing** agents when administered to human patients and animal models displaying noninsulin-dependent **diabetes** mellitus. In Zucker rats, the **antidiabetic** activity is assocd. with increased glucose uptake in adipose tissue. To understand the direct effects **Troglitazone** has on adipocyte metab., 3T3-L1 preadipocytes and adipocytes were **treated** with the compd. The addn. of **Troglitazone** enhanced the rate and percent differentiation of fibroblasts to adipocytes. Northern anal. indicated that during differentiation, expression of the adipocyte-specific transcription factor, CCAAT enhancer binding protein-.alpha., increased more rapidly in **Troglitazone-treated** cells, but did not change in fully differentiated adipocytes. To assess the metabolic consequences of **Troglitazone treatment**, both basal and insulin-stimulated glucose uptake were monitored in **treated** cells. **Troglitazone treatment** increased basal glucose transport 1.5- to 2.0-fold, whereas insulin-stimulated uptake was unaffected. Enhanced basal transport was caused by an increased synthesis of both Glut1 glucose transporter mRNA and protein. These results suggest the possibility that in vivo, the **Troglitazone**-dependent increase in glucose disposal may be attributable in part to modifications in the expression of Glut1 in insulin-responsive tissues.

IT 9004-10-8, **Insulin**, biological studies  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)  
(**Troglitazone** enhances differentiation, basal glucose uptake, and Glut1 protein levels in 3T3-L1 adipocytes)

L11 ANSWER 49 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1996:517811 HCAPLUS  
DOCUMENT NUMBER: 125:185520  
TITLE: Induction of uncoupling protein in brown adipose tissue. Synergy between norepinephrine and **pioglitazone**, an insulin-**sensitizing** agent

AUTHOR(S): Foellmi-Adams, Lisa A.; Wyse, Beatrice M.; Herron, David; Nedergaard, Jan; Kletzien, Rolf F.  
CORPORATE SOURCE: Endocrine Pharmacology Metabolism, Pharmacia & Upjohn Inc., Kalamazoo, MI, 49001, USA  
SOURCE: Biochem. Pharmacol. (1996), 52(5), 693-701  
CODEN: BCPA6; ISSN: 0006-2952  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Insulin resistance and obesity in rodent models of non-insulin-dependent **diabetes** mellitus have been correlated with ablated or defective brown adipose tissue (BAT) function. The mitochondrial uncoupling protein (UCP) allows BAT to perform its unique role in facultative energy expenditure. In this study, we obsd. an increase in both BAT mass and the expression of UCP mRNA in BAT from obese **diabetic** mice and their lean littermates following **treatment** with the thiazolidinedione **pioglitazone**, a novel insulin-**sensitizing** agent. Thus, we wanted to ascertain if **pioglitazone** directly induces BAT differentiation. We found that **treatment** for 48 h with **pioglitazone** caused a 32-fold increase in UCP mRNA, whereas a 7-h **treatment** with norepinephrine caused a 24-fold increase in expression. Cells **treated** with **pioglitazone** for 48 h, with norepinephrine added during the last 7 h, demonstrated a 59-fold increase in UCP mRNA. However, simultaneous **treatment** with **pioglitazone** and repeated **treatment** norepinephrine for 48 h yielded a greater than 200-fold increase in UCP mRNA. Examn. of UCP

protein levels demonstrated a similar time-dependent increase with **pioglitazone** and/or norepinephrine **treatment**, as well as a synergistic increase with concurrent **pioglitazone** and norepinephrine **treatment**. This study shows that **pioglitazone** exerts a direct effect on BAT cells in vitro by increasing UCP mRNA protein protei and protein levels, and that it also synergizes with norepinephrine perhaps by inducing and stabilizing UCP mRNA and/or preventing proteolysis of UCP protein.

L11 ANSWER 50 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:902136 HCAPLUS

DOCUMENT NUMBER: 123:311577

TITLE: Compensatory alterations for insulin signal transduction and glucose transport in insulin-resistant **diabetes**

AUTHOR(S): Bonini, James A.; Colca, Jerry R.; Dailey, Charlene; White, Morris; Hofmann, Cecilia

CORPORATE SOURCE: Dep. Mol. Cell. Biochem., Loyola Univ. Stritch Sch. Med., Maywood, IL, 60153, USA

SOURCE: Am. J. Physiol. (1995), 269(4, Pt. 1), E759-E765  
CODEN: AJPHAP; ISSN: 0002-9513

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Insulin binding activates the receptor tyrosine kinase toward the insulin receptor substrate-1 (IRS-1). Phosphorylated IRS-1 then interacts with the p85.alpha. subunit of phosphatidylinositol 3-kinase (PI3K), Nck, growth factor receptor-bound protein 2 (GRB2), and Syp, thus branching insulin's signal for both mitogenic and metabolic responses. To det. whether the expression of these proteins is altered in insulin resistance, the levels of these proteins were compared in adipose and liver tissues of **nondiabetic** mice and obese insulin-resistant **diabetic** KKAY mice. IR and PI3K p85.alpha. protein levels were significantly lower in KKAY mice than in control **nondiabetic** mice, whereas IRS-1 protein levels were not altered. In contrast, the protein levels of GRB2, Nck, Syp, and GLUT-1 were dramatically elevated in KKAY fat, with less striking changes in liver. **Treatment** of **diabetic** animals with **pioglitazone**, an **insulin-sensitizing** antihyperglycemic agent, partially cor. the expression of some of these proteins. Taken together, these findings suggest that the insulin-resistant **diabetic** condition is characterized by changes in expression of insulin signal transduction components that may be assocd. with altered glucose metab.

L11 ANSWER 51 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:835683 HCAPLUS

DOCUMENT NUMBER: 123:218420

TITLE: Use of insulin sensitizers for **treating** renal diseases

INVENTOR(S): Buckingham, Robin Edwin

PATENT ASSIGNEE(S): Smithkline Beecham PLC, UK

SOURCE: PCT Int. Appl., 25 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9521608	A1	19950817	WO 1995-EP441	19950207
W:	AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US			
RW:	KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN,			

TD, TG

CA 2182986	AA 19950817	CA 1995-2182986	19950207
AU 9515783	A1 19950829	AU 1995-15783	19950207
AU 700826	B2 19990114		
HU 74382	A2 19961230	HU 1996-2207	19950207
CN 1145027	A 19970312	CN 1995-192362	19950207
EP 777469	A1 19970611	EP 1995-907653	19950207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE			
JP 09512249	T2 19971209	JP 1995-520956	19950207
ZA 9501002	A 19960808	ZA 1995-1002	19950208
PRIORITY APPLN. INFO.:		GB 1994-2624	19940210
		GB 1994-10214	19940521
		GB 1994-26019	19941222
		WO 1995-EP441	19950207

OTHER SOURCE(S): MARPAT 123:218420

AB A method for the **treatment** and/or prophylaxis of renal diseases including **diabetic** nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease, and microalbuminuria which method comprises the administration of an effective, non-toxic amt. of an insulin sensitizer to a human or non-human mammal in need thereof. An example compd. is 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione.

IT **122320-73-4, BRL 49653**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**insulin sensitizers** for **treating** renal diseases)

L11 ANSWER 52 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:805293 HCAPLUS

DOCUMENT NUMBER: 123:246544

TITLE: Repeat **treatment** of obese mice with**BRL 49653**, a new and potent**insulin sensitizer**, enhances insulin

action in white adipocytes. Association with increased insulin binding and cell-surface GLUT4 as measured by photoaffinity labeling

AUTHOR(S): Young, Paul W.; Cawthorne, Michael A.; Coyle, Paul J.; Holder, Julie C.; Holman, Geoffrey D.; Kozka, Izabela J.; Kirkham, David M.; Lister, Carolyn A.; Smith, Stephen A.

CORPORATE SOURCE: SmithKline Beecham Pharmaceuticals, Epsom/Surrey, UK

SOURCE: Diabetes (1995), 44(9), 1087-92

CODEN: DIAEAZ; ISSN: 0012-1797

DOCUMENT TYPE: Journal

LANGUAGE: English

AB (.-)-5-([4-[2-Methyl-2(pyridinylamino)ethoxy]phenyl]methyl) 2,4-thiazolidinedione (BRL 49543) is a new potent **antidiabetic** agent that improves insulin sensitivity in animal models of NIDDM. In C57BL/6 obese (ob/ob) mice, BRL 49653, included in the diet for 8 days, improved glucose tolerance. The half-maximal ED was 3 .mu.mol/kg diet, which is equiv. to .apprx.0.1 mg/kg body wt. Improvements in glucose tolerance were accompanied by significant redns. in circulating triacylglycerol, nonesterified fatty acids, and insulin. The insulin receptor no. of epididymal white adipocytes prep. from obese mice **treated** with BRL 49653 (30 .mu.mol/kg diet) for 14 days was increased twofold. The affinity of the receptor for insulin was unchanged. In the absence of added insulin, the rates of glucose transport in adipocytes from untreated and BRL 49653-**treated** obese mice were similar. Insulin (73 nmol/l) produced only a 1.5-fold increase in glucose transport in adipocytes from control obese mice, whereas after **BRL 49653 treatment**, **insulin** stimulated glucose transport 2.8-fold. BRL 49653 did not alter the sensitivity of glucose transport to insulin. The increase in insulin responsiveness was accompanied by a 2.5-fold increase in the total tissue content of the glucose transporter GLUT4. Glucose transport in

adipocytes from lean littermates was not altered by BRL 49653. To establish the contribution of changes in glucose transporter trafficking to the **BRL 49653**-mediated increase in **insulin** action, the cell-impermeant bis-mannose photolabel 2-N-[4-(1-azi-2,2,2-trifluoroethyl)benzoyl]-1,3-bis(D-mannos-4-yloxy)-2-[2-3H]-propylamine was used to measure adipocyte cell surface-assocd. glucose transporters. In these expts., the increase in maximal insulin stimulated glucose transport (4.2-fold) produced after BRL 49653 **treatment** was correlated with a 2.6-fold increase in cell-surface-assocd. GLUT4. Photolabeled cell-surface GLUT1 was not detectable in any adipocyte prepn. These results suggest that the improvement in glycemic control produced by repeated administration of BRL 49653 to obese mice is mediated by increased insulin responsiveness of target tissues. **BRL 49653** potentiates **insulin**-stimulated glucose transport in adipocytes from insulin-resistant obese mice, both by increasing insulin receptor no. and by facilitating translocation of GLUT4, from an expanded intracellular pool, to the cell surface. In addn., the increased intrinsic activity of cell-surface glucose transporters may also contribute to an increased insulin responsiveness of adipose tissue.

IT 9004-10-8, **Insulin**, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)

(**antidiabetic BRL 49653** increases

**insulin** binding and cell-surface GLUT4 in adipocytes of obese mice)

L11 ANSWER 53 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:740451 HCAPLUS

DOCUMENT NUMBER: 123:160582

TITLE: Insulin secretory defect in Zucker fa/fa rats is improved by ameliorating insulin resistance

AUTHOR(S): de Souza, Christopher J.; Yu, Jen H.; Robinson, Deborah D.; Ulrich, Roger G.; Meglasson, Martin D.

CORPORATE SOURCE: Department of Endocrine Pharmacology and Metabolism, Upjohn Laboratories, Kalamazoo, MI, 49001, USA

SOURCE: Diabetes (1995), 44(8), 984-91

CODEN: DIAEAZ; ISSN: 0012-1797

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The role of insulin resistance in the impaired glucose-stimulated insulin release of Zucker fatty rats was investigated using the **insulin-sensitizing** thiazolidinedione **drug pioglitazone**

. Fatty rats had fasting hyperinsulinemia yet a blunted secretory response to i.v. glucose compared with lean age-matched controls. Islets from fatty rats secreted less insulin (based on islet DNA) in response to high glucose than islets from lean rats but secreted normal amts. of insulin when tolbutamide or .alpha.-ketoisocaproic acid (.alpha.-KIC) was the stimulus. Administering **pioglitazone** for 9 days diminished basal **hyperinsulinemia** and increased the insulin response to high glucose by fatty rats but not by lean controls. **Pioglitazone** pretreatment augmented the secretory response by isolated islets to high glucose, .alpha.-KIC, and tolbutamide. Augmentation of islet insulin release was not assocd. with reduced plasma glucose concn., suggesting that altered glycemia was not involved. Pancreas and islet insulin content was greater in fatty rats than in lean controls and was decreased by **pioglitazone**; hence, **insulin** stores and glucose-stimulated insulin release did not correlate.

**Pioglitazone treatment** did not affect the rate of islet glucose usage or ATP/ADP in the presence of 2.75 or 16 mmol/l glucose. These data indicate that ameliorating insulin resistance reverses defective glucose-stimulated insulin release by Zucker fa/fa rats. After **pioglitazone** administration, **insulin** secretion may be augmented by increased generation of a metabolic coupling factor from glucose or at a later step in the secretory process that is common to both glucose and nonglucose secretagogues.

IT 111025-46-8, **Pioglitazone**

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(**insulin** secretory defect in Zucker fa/fa rats is improved by  
ameliorating **insulin** resistance with **pioglitazone**)

L11 ANSWER 54 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:437097 HCAPLUS

DOCUMENT NUMBER: 122:204899

TITLE: Insulin sensitization in **diabetic** rat liver  
by an antihyperglycemic agent

AUTHOR(S): Hofmann, Cecilia; Lorenz, Kathryn; Williams, David;  
Palazuk, Barbara J.; Colca, Jerry R.

CORPORATE SOURCE: Metabolic Diseases Research Unit, The Upjohn Company,  
Kalamazoo, MI, USA

SOURCE: Metab., Clin. Exp. (1995), 44(3), 384-9

CODEN: METAAJ; ISSN: 0026-0495

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study aimed to demonstrate directly that the thiazolidinedione  
**pioglitazone** acts as an **insulin sensitizer**.

The hypothesis was tested that **pioglitazone treatment**  
of **diabetic** rats alters liver function such that responsiveness  
of selected genes to subsequent insulin regulation is enhanced. Although  
flux through gluconeogenic/glycolytic pathways involves regulation of many  
enzymes, this study reports the effects of insulin on expression of 2 key  
enzymes in these metabolic pathways, i.e., phosphoenolpyruvate  
carboxykinase (PEPCK) and glucokinase (GK). Rats were used either as  
**nondiabetic** controls or injected with streptozotocin as a model  
for insulin-deficient **diabetes**. **Diabetic** animals were  
**treated** without or with **pioglitazone** and subsequently  
examd. for acute responses to insulin. **Pioglitazone**  
**treatment** of **diabetic** animals enhanced the ability of  
insulin to reverse elevated blood glucose. Although the mean level of  
liver mRNA transcripts encoding PEPCK was increased to nearly 300% in  
**diabetic** animals as compared with **nondiabetic** controls  
(100%), it was lower in **pioglitazone-treated**  
**diabetic** rats (119% of control) than in **diabetic** rats  
without **pioglitazone** (223% of control) after **insulin**  
**treatment**. By contrast, mRNA transcripts encoding GK were not  
detectable in **diabetic** animals, but were increased markedly by  
insulin **treatment** in all the animals. Insulin-enhanced  
expression of GK was greater in liver from animals **treated**  
earlier with **pioglitazone** (291% of control) than in liver from  
those that were untreated (214% of control). The amplified acute response  
of the liver to **insulin** thus established **pioglitazone**  
as an **insulin sensitizer**. The findings further showed  
that such **sensitization** can be developed even in the  
insulin-deficient state. These observations underscore the potential for  
agents with this action to reverse the insulin-resistant state  
characteristic of non-insulin-dependent **diabetes**.

IT 111025-46-8, **Pioglitazone**

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)

(**insulin sensitization** in **diabetic** liver  
by **pioglitazone**)

L11 ANSWER 55 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1994:595573 HCAPLUS

DOCUMENT NUMBER: 121:195573

TITLE: Potentiation of insulin stimulation of  
phosphatidylinositol 3-kinase by thiazolidinedione-  
derived **antidiabetic** agents in Chinese  
hamster ovary cells expressing human insulin receptors  
and L6 myotubes

AUTHOR(S): Zhang, Bei; Szalkowski, Deborah; Diaz, Elva; Hayes,  
Nancy; Smith, Roy; Berger, Joel

CORPORATE SOURCE: Dep. Mol. Endocrinol., Merck Res. Lab., Rahway, NJ,  
07065, USA  
SOURCE: J. Biol. Chem. (1994), 269(41), 25735-41  
CODEN: JBCHA3; ISSN: 0021-9258  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Thiazolidinedione derivs. are insulin-**sensitizing** agents with proven **antidiabetic** activities in vivo. To explore the mechanism of action of this class of compds., the effects of **pioglitazone**, CP-86,325 (CP), and AD-5075 on elements of the insulin signal transduction pathways were studied in Chinese hamster ovary cells overexpressing human insulin receptor (CHO.cntdot.T) and L6 myotubes. In CHO.cntdot.T cells, the binding of insulin to its receptor and the insulin-stimulated tyrosine kinase activity of the receptor were not altered by **pioglitazone** or CP-86,325. In contrast, **treatment** of CHO.cntdot.T cells with the compds. resulted in significant increases in insulin-stimulated phosphatidylinositol (PI) 3-kinase activity. This insulin-enhancing effect was also obsd. in L6 myotubes **treated** with CP-86,325. The augmentation in kinase activity obsd. in CHO.cntdot.T cells correlated with increases in the amt. of PI-3-kinase (p85 subunit) in anti-phosphotyrosine immunoppts. of cell lysates. No gross changes in the tyrosine phosphorylation state of the insulin receptor substrate-1 were detected in insulin-stimulated CHO.cntdot.T cells following **treatment** with the compds. Furthermore, the compds. did not enhance insulin stimulation of mitogen-activated protein kinase or DNA synthesis in CHO.cntdot.T cells. Thus, thiazolidinedione-derived **antidiabetic** agents may act as insulin **sensitizers** by augmenting insulin stimulation of PI-3-kinase activity in a rather specific manner.

IT 111025-46-8, **Pioglitazone**

RL: BIOL (Biological study)  
(**insulin** stimulation of phosphatidylinositol kinase  
potentiation by, **antidiabetic** activity in relation to)

L11 ANSWER 56 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1994:235869 HCAPLUS  
DOCUMENT NUMBER: 120:235869  
TITLE: Localization of a pioglitazone response element in the  
adipocyte fatty acid-binding protein gene  
AUTHOR(S): Harris, Peter K. W.; Kletzien, Rolf F.  
CORPORATE SOURCE: Upjohn Lab., Upjohn Co., Kalamazoo, MI, 49001, USA  
SOURCE: Mol. Pharmacol. (1994), 45(3), 439-45  
CODEN: MOPMA3; ISSN: 0026-895X  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The thiazolidinediones are a class of **antidiabetic** compds. that increase the sensitivity of target tissues to insulin. An earlier study has shown that these compds. enhance the insulin-stimulated differentiation of 3T3-L1 cells and up-regulate expression of differentiation-dependent genes. The authors have obsd. that the mRNA encoding the adipocyte fatty acid-binding protein (aFABP) increases shortly after incubation of cells with **pioglitazone**, a thiazolidinedione analog. The **drug** was found to enhance, in a time- and dose-dependent fashion, the expression of a chimeric gene that was constructed by fusing the aFABP promoter upstream of the chloramphenicol acetyltransferase (CAT) gene. To localize the sequence within the promoter that is responsive to **pioglitazone**, a series of chimeric genes contg. sections of the aFABP promoter fused to the CAT gene were analyzed after transfection of 3T3-L1 cells. A section of DNA located at -5.2 kilobases and known to encompass a tissue-specific and differentiation-dependent enhancer element was found to confer responsiveness to the **drug**. Anal. of sequences in this region of the aFABP promoter by DNA gel retardation assays revealed the presence of a protein in nuclear exts. from **drug-treated** cells that bound to a specific sequence (ARE-6). The presence of the protein could be demonstrated in differentiated adipocytes, but the protein was



present at only two levels in preadipocytes. **Treatment** of preadipocytes with **pioglitazone** resulted in the precocious appearance of this protein in nuclear exts. Multiple copies of the ARE-6 sequence inserted upstream of a heterologous promoter linked to the CAT gene conferred **pioglitazone** responsiveness. The expts. reported in this study establish that the **insulin-sensitizing** agent **pioglitazone** up-regulates expression of the aFABP gene from an element located within a region of DNA responsible for tissue-specific and differentiation-dependent expression of the gene.

L11 ANSWER 57 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1994:208333 HCAPLUS

DOCUMENT NUMBER: 120:208333

TITLE: Pioglitazone inhibits the **diabetogenic** action of growth hormone, but not its ability to promote growth

AUTHOR(S): Towns, Roberto; Kostyo, Jack L.; Colca, Jerry R.

CORPORATE SOURCE: Dep. Physiol., Univ. Michigan, Ann Arbor, MI, 48109, USA

SOURCE: Endocrinology (1994), 134(2), 608-13

CODEN: ENDOAO; ISSN: 0013-7227

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Analogs of triazolidinedione improve the responsiveness of insulin-resistant animals to insulin. One such analog, **pioglitazone** (5-{4-[2-(5-ethyl-2-pyridinyl)ethoxy]benzyl}thiazolidine-2,4-dione hydrochloride), when fed to insulin-resistant animals such as the obese (ob/ob) mouse, reduces blood glucose and lipids and also lowers the plasma insulin level. Because GH can produce insulin resistance in humans and animals such as the ob/ob mouse, the present study was conducted to det. whether feeding **pioglitazone** can (1) inhibit the ability of GH to induce enhanced insulin resistance in obese mice, (2) ameliorate or reverse GH-induced insulin resistance once it has been in ob/ob mice, and (3) alter the ability of GH to promote growth in hypophysectomized rats. Female ob/ob mice were fed a control diet or a diet contg. **pioglitazone** (20 mg/kg animal.cntdot.day) for 4 days. During the last 3 days of the feeding period, the mice also received a daily s.c. injection of either saline or 200 .mu.g S-carboxymethylated human GH (RCM-hGH), which is a GH deriv. having mainly **diabetogenic** activity. In control-fed mice, RCM-hGH increased blood glucose and plasma insulin levels, which is an expected response to GH-induced insulin resistance. By contrast, the ability of RCM-hGH to increase blood glucose and plasma **insulin** levels was totally blocked in **pioglitazone**-fed mice. To det. whether **pioglitazone** can ameliorate GH-induced **insulin** resistance once it has been established, ob/ob mice were **treated** s.c. with either saline or 200 .mu.g RCM-hGH for 3 days. Half of the saline-**treated** and half of the hormone-**treated** mice were then fed **pioglitazone**, whereas the remaining animals were continued on the control diet. After 48 h on the diets, the blood glucose and plasma insulin levels of the RCM-hGH **treated** mice fed the control diet remained elevated with respect to those in the saline-**treated** controls. On the other hand, the blood glucose and plasma insulin levels of the RCM-hGH **treated** mice fed **pioglitazone** were markedly reduced compared to those of the RCM-hGH-**treated** control-fed animals. Thus, these results suggest that **pioglitazone** can ameliorate GH-induced **insulin** resistance. To det. whether **pioglitazone** interferes with the growth-promoting activity of GH, male hypophysectomized rats were fed **pioglitazone** or a control diet for 2 wk and then given a daily s.c. injection of 0, 10, or 50 .mu.g hGH for 9 days. **Pioglitazone** feeding was continued during this **treatment**. Wt. gain in response to hGH did not differ between the control and **pioglitazone**-fed groups. There was also no difference in total food consumption (grams of chow per g rat) among the groups, and plasma triglyceride levels were significantly lower in the

rats fed **pioglitazone**. These findings indicate that **pioglitazone** can counteract the **diabetogenic** action of GH without affecting its ability to promote growth and suggest that such insulin-**sensitizing** agents might be used **therapeutically** to minimize the **diabetogenic** action of GH.

IT 111025-46-8, **Pioglitazone**

RL: BIOL (Biological study)

(**insulin** resistant **diabetogenic** action of growth hormone inhibition by)

L11 ANSWER 58 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1994:97018 HCAPLUS

DOCUMENT NUMBER: 120:97018

TITLE: Altered gene expression for tumor necrosis factor-.alpha. and its receptors during **drug** and dietary modulation of insulin resistance

AUTHOR(S): Hofmann, Cecilia; Lorenz, Kathryn; Braithwaite, Susan S.; Colca, Jerry R.; Palazuk, Barbara J.; Hotamisligil, Goekhan S.; Spiegelman, Bruce M.

CORPORATE SOURCE: Res. Serv., Hines Vet. Adm. Hosp., Hines, IL, 60141, USA

SOURCE: Endocrinology (1994), 134(1), 264-70

CODEN: ENDOAO; ISSN: 0013-7227

DOCUMENT TYPE: Journal

LANGUAGE: English

AB As obesity is a major risk factor for noninsulin-dependent **diabetes** mellitus, adipose tissue may generate a mediator that influences the activity of insulin on various target tissues. Recent evidence suggests that a cytokine, tumor necrosis factor-.alpha. (TNF-.alpha.), may serve this role. This study investigates whether the expression of TNF.alpha. and its receptors is modulated during **drug treatment** to reduce insulin resistance. The effects of moderate wt. loss by dietary restriction were also examd. The authors show here that a marked induction of TNF.alpha. mRNA occurs in adipose tissues from a mouse model of obesity-linked **diabetes** (KKay) compared to that in **nondiabetic** mice (C57). Likewise, RNA transcripts encoding TNF R2 receptors (p75) were significantly increased in fat tissues of the obese **diabetic** animals. In muscle from these **diabetic** animals, RNA transcripts encoding both TNF R1 (p55) and R2 were significantly elevated, although R2 transcript abundance was less elevated than in fat. The authors also obsd. that the overexpression of mRNA for TNF.alpha. and both of its receptors could be at least partly normalized by **treatment** of the **diabetic** animals with the **insulin-sensitizing** agent **pioglitazone**. **Treating** of the obese **diabetic** animals by food restriction reduced the expression of mRNA for TNF R2 in muscle, but not fat. These results clearly indicate that gene expression for the TNF systems can be regulated by an insulin-**sensitizing drug** and redn. of body wt. Such findings support a role for this cytokine in the insulin-resistant **diabetic** state and show its modulation by **therapies** that reverse the disorder.

L11 ANSWER 59 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1993:446860 HCAPLUS

DOCUMENT NUMBER: 119:46860

TITLE: Lipoprotein profile characterization of the KKAY mouse, a rodent model of type II **diabetes**, before and after **treatment** with the **insulin-sensitizing** agent **pioglitazone**

AUTHOR(S): Castle, Christine K.; Colca, Jerry R.; Melchior, George W.

CORPORATE SOURCE: Metab. Dis. Res., Upjohn Lab., Kalamazoo, MI, USA

SOURCE: Arterioscler. Thromb. (1993), 13(2), 302-9

CODEN: ARTTE5; ISSN: 1049-8834

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study was to characterize the lipoprotein profile in the KKAY mouse, a rodent model of type II **diabetes**, before and after **treatment** with the **insulin-sensitizing drug pioglitazone**. Anal. of the plasma from untreated KKAY mice showed that they were severely hyperglycemic, severely hypertriglyceridemic, and moderately hypercholesterolemic. Agarose column chromatog. showed that essentially all of the triglycerides eluted with very-low-d. lipoprotein, and the majority of the cholesterol eluted with high-d. lipoprotein. Thus, both the very-low-d. lipoprotein and high-d. lipoprotein levels were markedly elevated in KKAY mice. Anal. of the lipoproteins by agarose electrophoresis-immunoblotting showed that apoprotein A-I and apoprotein B had aberrant electrophoretic behavior, typical of apoproteins that have been modified by nonenzymic glycosylation. **Treatment** of KKAY mice with **pioglitazone** for 8 days caused a marked redn. in blood glucose and plasma triglyceride concns. but had no effect on plasma cholesterol concn. or distribution. The aberrant electrophoretic behavior of the apoproteins was cor. to normal by **drug treatment**. These data show that the KKAY mouse has a severe dyslipoproteinemia that is probably secondary to its insulin resistance, but that its lipoprotein profile differs significantly from that of the insulin-resistant human in that the majority of the plasma cholesterol is carried in high-d. lipoprotein, and those high-d. lipoprotein levels are very high.

L11 ANSWER 60 OF 60 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1993:139604 HCAPLUS

DOCUMENT NUMBER: 118:139604

TITLE: Adipocyte fatty acid-binding protein: regulation of gene expression in vivo and in vitro by an insulin-sensitizing agent

AUTHOR(S): Kletzien, Rolf F.; Foellmi, Lisa A.; Harris, Peter K. W.; Wyse, Beatrice M.; Clarke, Steven D.

CORPORATE SOURCE: Upjohn Lab., Upjohn Co., Kalamazoo, MI, 49001, USA

SOURCE: Mol. Pharmacol. (1992), 42(4), 558-62

CODEN: MOPMA3; ISSN: 0026-895X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pioglitazone, a thiazolidinedione, is a novel **antidiabetic** compd. that can lower blood glucose in **diabetic** rodents by increasing insulin sensitivity in target tissues. The authors previously demonstrated that **pioglitazone** can enhance the **insulin** - or **insulin**-like growth factor-1-regulated differentiation of 3T3-L1 cells, a cell line that undergoes morphol. and biochem. differentiation to mature adipocytes. In this study, the authors examd. the effect of pioglitazone on the expression of the adipocyte fatty acid-binding protein (aFABP) in ob/ob mice and 3T3-L1 cells. Administration of the **drug** to mice was obsd. to cause a dose-dependent increase in aFABP mRNA expression in epididymal fat, which was correlated with a decrease in blood glucose and insulin levels. **Treatment** of 3T3-L1 cells with pioglitazone enhanced aFABP expression in a time-dependent fashion. To explore a possible direct effect of pioglitazone on aFABP expression, a chimeric gene was constructed contg. that aFABP promoter fused upstream of the bacterial reporter gene for chloramphenicol acetyltransferase. After transfection into 3T3-L1 cells and selection of stable transformants, regulation of the chimeric gene was studied. **Pioglitazone**, in combination with **insulin** or **insulin**-like growth factor-1, was obsd. to elicit a dose-dependent increase in expression, indicating a role for pioglitazone in regulating transcription of the aFABP gene. Several thiazolidinedione analogs were tested for their ability to induce the expression of the chimeric gene, and it was found that activity in this assay paralleled the structure-activity relationships obsd. for enhancement of 3T3-L1 cell differentiation. These observations on control of aFABP gene expression by pioglitazone suggest possible mechanisms by

which cellular sensitivity to insulin may be regulated.

IT 111025-46-8, **Pioglitazone**

RL: BIOL (Biological study)

(fatty acid-binding protein expression stimulation by, in adipocytes,  
insulin **sensitization** and **antidiabetic** mechanism in  
relation to)

L15 ANSWER 1 OF 10 USPATFULL  
AN 1999:124920 USPATFULL ✓  
TI Pharmaceutical composition  
IN Ikeda, Hitoshi, Higashiosaka, Japan  
Sohda, Takashi, Takatsuki, Japan  
Odaka, Hiroyuki, Kobe, Japan  
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)  
PI US 5965584 19991012  
AI US 1998-57465 19980409 (9)  
RLI Division of Ser. No. US 1996-667979, filed on 19 Jun 1996  
PRAI JP 1995-153500 19950620  
DT Utility  
LN.CNT 1220  
INCL INCLM: 514/342.000  
INCLS: 514/340.000; 514/365.000; 514/374.000; 546/269.700; 546/271.400;  
548/146.000; 548/215.000  
NCL NCLM: 514/342.000  
NCLS: 514/340.000; 514/365.000; 514/374.000; 546/269.700; 546/271.400;  
548/146.000; 548/215.000  
IC [6]  
ICM: A61K031-425  
ICS: A61K031-44; A61K045-06  
EXF 546/269.7; 546/271.4; 514/342; 514/340; 514/365; 514/374; 548/146;  
548/215  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 2 OF 10 USPATFULL ✓  
AN 1999:4694 USPATFULL  
TI Sulfonylurea-glitazone combinations for diabetes  
IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States  
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)  
PI US 5859037 19990112  
AI US 1997-970057 19971113 (8)  
PRAI US 1997-38224 19970219 (60)  
DT Utility  
LN.CNT 1902  
INCL INCLM: 514/369.000  
INCLS: 514/593.000; 514/866.000  
NCL NCLM: 514/369.000  
NCLS: 514/593.000; 514/866.000  
IC [6]  
ICM: A61K031-425  
ICS: A61K031-175  
EXF 514/369; 514/593; 514/866  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 3 OF 10 USPATFULL  
AN 1998:143665 USPATEFULL ✓  
TI Method of reducing blood glucose by administering Harunganin or Vismin  
IN Inman, Wayne DeWald, Belmont, CA, United States  
Luo, Jian, Brisbane, CA, United States  
PA Shaman Pharmaceuticals, Inc., South San Francisco, CA, United States (U.S. corporation)  
PI US 5837255 19981117  
AI US 1996-762785 19961210 (8)

DT Utility  
LN.CNT 1085  
INCL INCLM: 424/195.100  
INCLS: 514/003.000; 514/004.000; 514/323.000; 514/369.000; 514/635.000;  
514/680.000; 514/884.000; 552/271.000  
NCL NCLM: 424/195.100  
NCLS: 514/003.000; 514/004.000; 514/323.000; 514/369.000; 514/635.000;  
514/680.000; 514/884.000; 552/271.000  
IC [6]  
ICM: A61K035-78  
ICS: A61K038-28; A61K031-12; C07C050-18  
EXF 514/766; 514/680; 514/3; 514/4; 514/21; 514/53; 514/323; 514/635;  
514/369; 514/884; 552/271; 424/195.1  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 4 OF 10 USPATFULL  
AN 1998:48445 USPATFULL  
TI Furanoeremophilane and eremophilanolide sesquiterpenes for treatment of  
diabetes  
IN Inman, Wayne D., Belmont, CA, United States  
King, Steven Row, Moss Beach, CA, United States  
Evans, Joseph L., San Francisco, CA, United States  
Luo, Jian, Brisbane, CA, United States  
PA Shaman Pharmaceuticals, Inc., South San Francisco, CA, United States  
(U.S. corporation)  
PI US 5747527 19980505  
AI US 1995-479049 19950606 (8)  
DT Utility  
LN.CNT 1203  
INCL INCLM: 514/453.000  
INCLS: 514/468.000  
NCL NCLM: 514/453.000  
NCLS: 514/468.000  
IC [6]  
ICM: A61K031-35  
ICS: A61K031-355  
EXF 514/453; 514/468  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 5 OF 10 USPATFULL  
AN 1998:4611 USPATFULL  
TI Use of thiazolidinedione derivatives and related antihyperglycemic  
agents in the treatment of insulin resistant subjects with normal  
glucose tolerance in order to prevent or delay the onset of  
noninsulin-dependent mellitus  
IN Olefsky, Jerrold M., Solana Beach, CA, United States  
PA Sankyo Company, Limited, Tokyo, Japan (non-U.S. corporation)  
PI US 5708012 19980113  
AI US 1995-431266 19950428 (8)  
DT Utility  
LN.CNT 1393  
INCL INCLM: 514/337.000  
INCLS: 514/359.000; 514/369.000; 514/370.000; 514/439.000; 514/443.000;  
514/444.000; 514/455.000; 514/456.000  
NCL NCLM: 514/337.000  
NCLS: 514/359.000; 514/369.000; 514/370.000; 514/439.000; 514/443.000;  
514/444.000; 514/455.000; 514/456.000  
IC [6]  
ICM: A01N043-40  
EXF 514/337; 514/359; 514/369; 514/370; 514/439; 514/443; 514/444; 514/455;  
514/456  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 6 OF 10 USPATFULL  
AN 97:109942 USPATFULL

TI Triterpenoid compound for the treatment of diabetes  
IN Inman, Wayne D., Belmont, CA, United States  
Reed, Michael John, Menlo Park, CA, United States  
PA Shaman Pharmaceuticals, Inc., South San Francisco, CA, United States  
(U.S. corporation)  
PI US 5691386 19971125 ✓  
AI US 1996-633396 19960416 (8)  
DT Utility  
LN.CNT 553  
INCL INCLM: 514/691.000  
INCLS: 568/368.000  
NCL NCLM: 514/691.000  
NCLS: 568/368.000  
IC [6]  
ICM: A61K031-12  
EXF 514/691; 568/368  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 7 OF 10 USPATFULL

AN 97:91557 USPATFULL  
TI Terpenoid-type quinones for treatment of diabetes  
IN Ubillas, Rosa P., Foster City, CA, United States  
Shivanand, Jolad D., San Carlos, CA, United States  
Mendez, Christopher D., San Francisco, CA, United States  
Fort, Diana M., Pacifica, CA, United States  
Evans, Joseph L., San Francisco, CA, United States  
Luo, Jian, Brisbane, CA, United States  
PA Shaman Pharmaceuticals, Inc., South San Francisco, CA, United States  
(U.S. corporation)  
PI US 5674900 19971007  
AI US 1995-510025 19950801 (8)  
RLI Continuation-in-part of Ser. No. US 1995-471867, filed on 6 Jun 1995,  
now abandoned  
DT Utility  
LN.CNT 1133  
INCL INCLM: 514/557.000  
INCLS: 514/866.000; 514/680.000; 562/498.000; 562/503.000; 552/298.000  
NCL NCLM: 514/557.000  
NCLS: 514/680.000; 514/866.000; 552/298.000; 562/498.000; 562/503.000  
IC [6]  
ICM: A61K031-19  
ICS: A61K031-82; C07C050-34  
EXF 552/298; 514/557; 514/866; 514/680; 562/498; 562/503  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 8 OF 10 USPATFULL

AN 97:40797 USPATFULL  
TI Hypoglycemic agent from cryptolepis  
IN Luo, Jian, Brisbane, CA, United States  
Fort, Diana M., Pacifica, CA, United States  
Bierer, Donald E., Daly City, CA, United States  
Bruening, Reimar C., San Carlos, CA, United States  
PA Shaman Pharmaceuticals, Inc., South San Francisco, CA, United States  
(U.S. corporation)  
PI US 5629319 19970513 ✓  
AI US 1995-472036 19950606 (8)  
RLI Division of Ser. No. US 1994-314188, filed on 28 Sep 1994  
DT Utility  
LN.CNT 1309  
INCL INCLM: 514/284.000  
INCLS: 514/285.000; 514/410.000; 514/866.000; 514/884.000  
NCL NCLM: 514/284.000  
NCLS: 514/285.000; 514/410.000; 514/866.000; 514/884.000  
IC [6]  
ICM: A61K031-44

ICS: A61K031-40  
EXF 514/284; 514/285; 514/410; 514/866; 514/884  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 9 OF 10 USPATFULL  
AN 97:12471 USPATFULL  
TI Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of disease states at risk for progressing to noninsulin-dependent diabetes mellitus  
IN Antonucci, Tammy, Meguon, WI, United States  
Lockwood, Dean, Ann Arbor, MI, United States  
Norris, Rebecca, Kewadin, MI, United States  
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)  
PI US 5602133 19970211  
AI US 1995-469398 19950606 (8)  
RLI Division of Ser. No. US 1994-292585, filed on 23 Aug 1994, now patented,  
Pat. No. US 5457109 which is a continuation-in-part of Ser. No. US 1993-122251, filed on 15 Sep 1993, now abandoned  
DT Utility  
LN.CNT 1639  
INCL INCLM: 514/252.000  
INCLS: 514/256.000; 514/342.000; 514/360.000; 514/369.000  
NCL NCLM: 514/252.000  
NCLS: 514/256.000; 514/342.000; 514/360.000; 514/369.000  
IC [6]  
ICM: A61K031-425  
ICS: A61K031-41; A61K031-44; A61K031-42  
EXF 514/252; 514/256; 514/342; 514/360; 514/369  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 10 OF 10 USPATFULL  
AN 94:91070 USPATFULL  
TI Use of insulin sensitizing agents to treat hypertension  
IN Colca, Jerry R., Kalamazoo, MI, United States  
PA The Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)  
PI US 5356913 19941018  
AI US 1993-52216 19930422 (8)  
RLI Continuation of Ser. No. US 1992-919515, filed on 24 Jul 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-478090, filed on 9 Feb 1990, now abandoned  
DT Utility  
LN.CNT 208  
INCL INCLM: 514/342.000  
INCLS: 514/365.000; 514/866.000  
NCL NCLM: 514/342.000  
NCLS: 514/365.000; 514/866.000  
IC [5]  
ICM: A61K031-44  
ICS: A61K031-425  
EXF 514/340; 514/365; 514/370; 514/390; 514/342; 514/866  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.